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THE NEUROTIC CHILD

SOME FAMILIAR SYMPTOMS AND THEIR PROBLEMS *

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The intensive work done during the last twenty years on the functional nervous disorders of the adult has brought about a marked change of attitude in dealing with them. We are less inclined to attribute these disorders to hypothetical intoxications, nor are we satisfied with a mere reference to the basis of constitutional psychopathic inferiority on which they arise; the aim is now to find the meaning of each disorder, the rôle that it plays in the adaptation of the individual to the environment. We look on fever not as a disease, but as part of a mechanism of adaptation; so in a functional nervous disorder, whether it be a paralysis or blindness, morbid fears or obsessive thoughts or compulsive acts, we see adaptation to the complex environment, an adaptation which is inferior and unhygienic, but intelligible and often open to modification.

In studying these disorders, whether they belong to hysteria, the anxiety neuroses, the compulsion neuroses, or to less clearly defined neurasthenic and psychasthenic groups, one is compelled to go beyond the usual impersonal categories of internal medicine and to study the organized driving forces which are at the basis of human behavior. We are wont to assume that our judgments are the result of purely rational processes, that our actions are determined by purposes more or less clearly realized; we support our emotional prejudices by logical reasons, explain our preposterous behavior by the introduction of worthy motives, and in these reasons and motives our official personality finds much comfort. The unembarrassed study of the real biologic unit takes us beneath the surface to other dynamic factors, to more elemental and deeply rooted forces which drive us, but which we are used to ignore; we find that beneath the civilized surface the savage still survives, and the child may continue to direct the activity of the apparently emancipated adult.

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Neurotic symptoms to a large extent find their explanation in these underlying trends and among the determining factors of the symptoms a prominent place must be given to the attitudes, the problems and the conflicts of childhood. The psychopathologist is bound to have a keen interest in the problems of adaptation or behavior in childhood; he must observe the early indications of difficult adaptation, he must study the various types and early stages of unhygienic adaptation. The child, too, may then be found to have an unsuspected complexity of forces determining his behavior; here, too, the real biologic unit may be different from the conventional presentation, much more complicated than the cherub of the painter and the poet, or than the delightfully simple individuals who are supposed to inhabit our nurseries.

The recognition of this complexity may enable us to understand some of the nervous manifestations of childhood, which otherwise would be unintelligible. In this way the study of the adult and that of the child reinforce each other; beneath the adult reactions we can trace problems of the child, while the child's life at an early age may show indications of conflicts which tradition only admits in the adult. The psychopathologist, from his studies of the adult, is in a position to indicate to the pediatrist factors in the child which are apt to escape his notice, while the pediatrist has the opportunity of observing directly the reactions of the child and collecting material which will be of the greatest value to the psychopathologist.

A familiar situation may be chosen to illustrate the persistence of a childhood trend in adult life. The man of somewhat exaggerated independence, rather defiant toward teachers, heterodox in religion, very radical in politics, is inclined to explain his views as based on grounds of pure reason; but his general attitude of protest against authority may be merely the persistence of his old childhood conflict with the main authority of that period, the father. All trace of the original inarticulate feeling of protest may have been lost from consciousness, and yet it may survive and exert its influence beneath the conscious filial devotion of the adult. One does not have to look far to see examples of perplexing estrangement between father and son, mother and daughter; the antagonism is apt to be referred to some comparatively recent situation, and those concerned fail to see the childhood roots of the difficulty. It may, however, not be estrangement, but the reverse, that strikes us; there may be an excessive devotion and this may be the individual's defense against the latent disloyalty, as if the poor heir to a millionaire were to be morbidly worried about the trifling indisposition of the latter. Love and subconscious hate may be strangely blended and the devotion of the daughter to a mother, whose selfishness has dwarfed the girl's life, may draw its strength from both sources.

A girl marries an elderly and unsuitable husband to the bewilderment of her friends, who fail to appreciate at its true dynamic value the likeness of her husband, even in his faults, to the father, the object of her early devotion, and still the pattern by which unconsciously the emotional value to her of other men is determined.

These early affections may persist unmodified and direct the behavior of the adult to such a degree that we are entitled to look on this persistence as a neurotic symptom; it is an indication of the inability of the individual to pass from one phase of development to another, an evidence of want of emotional flexibility or maturity, a neurotic conservatism.

The persistence of this earlier attitude conflicts with the actual demands of the adult life; the man who unawares continues into his married life the affectionate attitude of the dependent child may be unable to account for strange difficulties of adaptation to married life, which find an expression in psychoneurotic symptoms.

This was the case in a married man of over 40, who was subject to periodic alcoholism, which masked recurrent moods of depression. An analysis of his case revealed the intimate relationship of these symptoms to the want of maturity of his emotional life, which had hampered his adjustment to married life. A cultured and apparently independent adult, he had much of the affectionate dependence of the child; although babified and protected from annoyances by his wife, he was not completely satisfied with her devotion, he grudged the love she gave her children, he seemed to crave some affection which he could not find, and at times in his moods of childlike desolation and helplessness he indulged in alcohol to excess. The basis for his unsatisfied longings seemed to be the persistence in his emotional life of the attitude of the child. From the age of 11 to 22 he had slept in the room of his widowed mother in order to attend to her invalid wants. When he was 22 an aunt said that she was going to wean him from his mother, and gave them rooms which were far apart. He became sleepless and lonesome, and it was to meet the sleeplessness which followed on this separation from his mother that his alcoholic indulgence owed its beginning.

The close relationship between his sleeplessness and his dependence on his mother was illustrated by an earlier episode. At the age of 17, on the death of his sister, he was sleepless for about a month; bromid failed to induce sleep; "the only way I could get sleep was to get into bed with my mother—it seemed to soothe me."

This neurotic exaggeration and persistence of the normal emotional dependence of the child on the mother could not be altogether laid at the door of unknown constitutional factors; it was no doubt fostered by the injudicious training given by the overaffectionate mother to her

only son. The mother probably did not realize that she might cultivate in her child a degree of emotional dependence which would be the dominant factor in his adult life and seriously interfere with his mature development. The patient himself had not realized the presence in his adult life of these driving forces, and derived immediate benefit from being put in a position to face clearly the actual factors underlying his difficulties in life.

The sleeplessness of this patient deserves attention; the comfort of the mother's presence responded to deep-seated cravings of his emotional life, which if left unsatisfied meant sleeplessness. In this case the situation was clear, and it is worth while keeping in mind the general principle that the sleeplessness of the neurotic adult may be due to obscure emotional cravings. The sleeplessness of the neurotic child, when separated from the mother's bed or room, may well be of similar origin; the temptation to resume the old sleeping arrangements may be great, but one must remember that the transition has to be made sometime and it is better to make it early than wait until habit has strengthened the emotional dependence.

The disproportionate or neurotic attachment for one parent may involve a converse antagonism to the other parent, it may be at the basis of jealousy of brother or sister, and these factors may express themselves indirectly in neurotic symptoms.

These facts may be granted to throw light on the neurotic disorders of the adult, but may seem of little application to the supposedly simple life of the child.

Before passing to the discussion of some cases which suggest that the same mechanisms are present in the child as in the adult, reference may be made to some other symptoms in the adult, as we shall meet similar symptoms in the case of the children.

A married woman of 32, never in love with her husband, with rather poor habits and standards, for some years had a rather intense sentimental relationship with a married man. About this time she began to show a quite exaggerated degree of personal cleanliness, washing her hands incessantly; the absurd but imperative cleanliness was the compensation for and indirect recognition of the underlying impurity which the patient did not care to face. The patient herself showed some insight into the mechanism of her disorder when she said, by way of spontaneous criticism of her symptoms, "It is better to have a clean soul than clean hands."

A similar explanation for the nervousness was found in the following case:

A schoolgirl of 16 began to fret about not being perfect in her school work, she read things over and over for fear she had not read them quite correctly; she wrote and rewrote letters; she showed a scrupulous worry about whether she had done her duty in asking her parents questions about her school plans.

This girl, with the obsessive striving for perfection in her less personal activities, had, as a matter of fact, been secretly living in a dissolute way for some time.

In the adult and the adolescent exaggerated standards frequently indicate the reaction of the personality to an underlying feeling of guilt, or discomfort, or inferiority; it is important to note that it is a reaction to this "feeling," not to the clearly recognized admission of these factors. There may be no clear recognition of them; consciousness may contain no direct trace of them; in fact the obsessive symptoms help to keep these intolerable elements from invading consciousness.

Such obsessive striving is not, however, limited to the adult and the adolescent; we find the same symptoms at an even earlier age.

A. G., a girl of 12, was brought to the dispensary of the Phipps Psychiatric Clinic Aug. 31, 1914.

The patient, a rather frail child, with some evidence of pulmonary tuberculosis, complained of many nervous symptoms. Her sleep was disturbed, and she had frequent night-terrors; she had distressing dreams of snakes and other animals, of the family being murdered, of her sister cutting her in pieces and sealing her up in cans. Even when awake at night she heard imaginary noises, such as bells ringing; she appeared also in her waking state to see animals chasing her. The mother suggested that these experiences might at least in part be misinterpretations of actual sounds.

During the following months the patient showed little improvement, the night-terrors and bad dreams persisted; on one occasion she talked of seeing snakes on the wall, and showed evidence of some suspicion, accusing her sister and mother of having talked about her.

In November the nervous symptoms were gone into more carefully. In sleep the patient tossed and tumbled in bed, but for some time had been free from bad dreams. If she read disturbing incidents in the paper, she slept worse at night. The mother, finding that she had to rise every night to quiet the patient, ended by taking the patient into her own bed and sleeping with her in her arms.

As to her morbid fears and scruples, she scrutinized every drop of water or milk to see that it was absolutely clean; she was afraid to eat if her hands had touched anything, and therefore was taking insufficient nourishment; she washed her hands constantly. In bed she worried over the possibility of having eaten anything without washing her hands; she was tormented by thoughts of having done something that might harm her, as, for example, "I think I swallowed a fly, will that hurt me?" She expressed fears of death, wondered if she had eaten enough to keep her alive till the morning. She fretted over minor acts of disobedience during the past day, and kept harping on them in distress "until the perspiration rolled off her." Every night she looked under the bed, fearing somebody might be there.

The patient was abnormally timid, hesitated to pick up a chicken for fear it might peck her. She was prudish and would not undress or bathe in the presence of her sister or mother. At the same time her timidity would not allow her to go to the outdoor toilet without her sister or mother coming in with her. Although at night she fretted over her disobedience and promised to amend her ways, in the daytime she was not very obedient, evaded all distasteful work, and the mother gave in to her "just to have peace."

During the following two months the patient on the whole slept somewhat better. She was now sleeping with her sister, but occasionally at night she

was scared and would call for her mother, wanting the latter to take her into her own bed. She still asked frequently if she were going to die, and at night asked if she would be well in the morning.

In January, 1915, the symptoms showed little change; at night, in bed with her mother, she spent over an hour asking incessantly whether she would be all right, whether she would die, whether anyone else of the family would fall sick. She discussed whether she had been sufficiently virtuous during the daytime, as, for example, "have I obeyed the doctor's orders and gone out enough today?"

In the daytime she was inseparable from her mother, would not go from one room to another without her. At her bath she insisted on being alone, but requested her mother to be in the adjoining room so that she could talk to her. She still scrutinized her food and drink very carefully, removed from her cereal any particle that was too brown; she washed her hands an unnecessary number of times.

During 1915 the patient made some improvement. Jan. 8, 1916, she was less timid and less prudish, did not cling so closely to her mother, in fact had on one occasion spent a whole afternoon with a friend away from her mother; previously she would not have thought of going anywhere without her mother. She now indulged in no unnecessary washing of hands, scrutinized her food less, and for some months had not asked if she was going to die. She still worried in an obsessive way about possible lapses, and at night repeated such questions as, "Am I a good girl?" The patient is now almost 14 years old and has not menstruated.

Can the obsessive cleanliness of this child, her exaggerated scruples as to her behavior, receive the same explanation as the same symptoms in the preceding cases? In that case we should assume an underlying feeling of discomfort with regard to personal factors, which the patient had not learned to face in a straightforward way. In the previous cases the personal conflict which was at the basis of the nervousness was in relation to the instinctive life, and it is possible that in the present case the same factors are at work, for the instinctive difficulties of the adult have their analogue in the life of the child. The patient was an extremely quiet and uncommunicative girl whose inner life it was not possible to fathom. In the treatment of such a case it is well to keep in mind the possibility that there are important trends beneath the surface, which do not express themselves directly; that these trends may have undue emotional value as a result of the influence of the environment; that the nervous symptoms may be merely a substitution or compensation for these subconscious factors. With this possibility in mind, the physician may do something to help the child toward a more healthy and open assimilation of factors, which to the child have presented an insoluble problem.

That we are not reading into the child's life a complexity of structure which only exists in the adult will be seen by some other cases, in which the underlying factors could be elicited. The problems presented by this girl of 12 have also cropped up in her cousin, a woman of 25.

The patient for more than a year had suffered from a morbid fear of contamination; this had developed after a bottle of douche medicine had been broken. The patient came to feel that everything might be contaminated, that she might carry the contamination to others; she was afraid to eat, for fear the dishes might not be clean; she slept for weeks on the couch for fear the bed might be contaminated; she sometimes spent eight hours out of the twenty-four in her ablutions. Out of her complete clinical history only one group of symptoms will be referred to, namely, those relating to her mother; these symptoms had made their first appearance at the age of 5 or 6. At that age, when she first went to school, she was accustomed to go half a block and then go back to ask her mother if she felt all right, if she felt she would die before the patient returned from school, if she were pleased, if she thought anything would happen, etc.; she sometimes repeated this performance two or three times before she arrived at the school.

In view of these symptoms we might be inclined to postulate merely a rather exaggerated emotional dependence of the child on her mother. The possibility of another interpretation is brought up by the following facts: This girl, with the great solicitude for her mother's welfare, from the age of 16 had tantrums in which she bit and scratched her mother, and called her "fool" and "devil." She had of recent years asked her mother somewhat perplexing questions, as, for example, "Mamma, do I wish you were dead? Would I rather have someone else for my mamma? Would I rather have you dead or living? Mamma, I don't mean that, do I? Is it just a bad thought?" The patient thought sometimes it was the devil that made her think those things.

Even before the age of 6 (the patient's statement) she often asked her mother if she were her mother's own child, or if she were an adopted child. Where do these elements come from that seem to contrast so strikingly with her official devotion to her mother? Must we assume that it is the devil at work, playing the same pranks he loves to play on conscientious ministers, who begin to find strange oaths and blasphemous remarks rising to their lips with obsessive force? In such cases a frank examination often shows that the life-long religious earnestness of the patient has developed partly as a defense against the recognition of elemental forces, which the individual obscurely feels can not be dealt with in the way that other human problems are met. So the neurotic devotion to the mother in the present case may be a defense against the recognition of a latent antagonism, which the personality feels itself unable to deal with. Such an antagonism may seem to some to be a rather rare perversion of the normal emotional life; on the contrary it is an inevitable result of the situation. The child seeks to assert itself, to dominate the environment, to live out its own natural trends, and in adapting itself to the necessary restrictions of an ethical environment it inevitably feels a restriction of its personality, and has some antagonism to the restricting forces. It is largely through the mother that the cultural environment brings its restrictions to bear on the child. So beneath the instinctive dependence and love of the child it is natural that we should find certain feelings of restriction and antagonism; and in the neurotic child both the oppos-

ing forces may have unusual strength, with symptoms such as those of the present case.

It may seem rather revolutionary to allow to a child of tender years an emotional life of such complexity, and it may appear especially difficult to accept such views in relation to the attitude of the child to the mother, where convention demands a unitary attitude of love.

The same peculiar blend of love and antagonism will perhaps be more readily admitted where we are dealing with a brother or sister, as in the following cases:

J. F., a boy of 7, was referred to the dispensary of the Phipps Psychiatric Clinic from the Harriet Lane Home, March 20, 1914. Following an attack of chickenpox in January he had shown peculiar nervous symptoms; previously of nice disposition, he was now rather irritable and sensitive; he did not want people to look at him and talk about him. Four days after recovery from the chickenpox he began to express odd ideas; he said that his feet were growing large and that his hands and nose and mouth were also increasing in size. After some time he ceased to express such ideas, but began to dream of snakes; he was now afraid to go into rooms alone, and one day when sent upstairs he was found shaking and crying, and claimed that he had seen a big black snake coming after him. He also dreamed of robbers. Some of his ideas seemed to depend partly on rather simple occurrences; thus, his fear that his nose was growing large may have been partly determined by the fact that his mother, when he had frequent nosebleed, had warned him not to touch his nose or it would get big. Other symptoms seemed to have a rather deeper origin. The boy dreamed of robbers, but in the dreams the robbers killed his little brother B., and cut him up in pieces; he also dreamed that B. was drowned. The mother stated that the patient was very fond of B., but she remembered that when B. was a little baby, and nursing, the patient, 5 years of age at the time, used to try to push B. away from her. The patient himself, in discussing B. with the physician, showed clear evidence of some jealousy; he said, "B. is the pet and sits in mother's lap; he is the pet because he always sleeps next to mother." The patient's jealousy of his little brother may also have been at the root of the feeling that he had been growing quite small, "like B."

In the robber dreams, in which his brother was removed, and in the dreams of B.'s death by drowning we see accomplished something which no doubt corresponded to the obscure longing of the boy, the removal of his rival in his mother's affection. Through the disguise of the dream one could see some of the important emotional factors in the boy's life. The symptoms had developed after the chickenpox and might be considered as in some vague way the expression of physical reduction; but the chickenpox had not only caused a fever, it had created a new situation. Before the chickenpox the mother and the children had slept in the same bed; on the onset of the chickenpox he was left alone in the bed, while his mother and little brother slept on the couch. It is therefore intelligible that the latent feeling of rivalry should be rendered keener by this new situation, and the dream may well have been the expression of those trends, which in the daytime were not allowed to express themselves directly.

Whatever the mechanism of the dreams, they at least guide us to important forces which otherwise might escape detection. They enable us to realize something of the complexity of the child's nature, to see beneath the simple and naïve surface repressed factors of great personal significance. Already at the age of 7, in his reaction to a trying emotional situation, we see that the child, in accepting that restriction of his emotional demands, which is involved in the equal demands of others, has difficulty; he develops peculiar reactions, which in a way give expression to the repressed trends.

For the treatment of such a case it is important to recognize the real factors involved and not to be satisfied with vague hypotheses as to toxic processes or with references to constitutional instability. It is true that such a reaction indicates that in face of a sufficiently banal situation the individual has not shown the normal degree of adaptability; the situation has been a test of the constitutional nervous stability of the individual. While this is true and while the constitutional limitations have to be recognized, the true nature of the test must not be overlooked, the possibility of making it less severe must be considered, and the way discussed in which the child with his constitutional lack of resistance may be trained to develop these special qualities, which are of importance in meeting personal problems. In that case the reference to a constitutional basis will not mean a fatalistic attitude, but will be followed by a keener sensitiveness to the problems of the child and a more enlightened way of dealing with them.

Here again light is thrown on normal psychology by the study of the reactions of the neurotic individual; the above case illustrates in a clear and dramatic way the presence of certain factors in the life of the normal child, which otherwise might escape us. The evidences of jealousy shown by normal children are often overlooked or are treated as rather amusing and negligible factors; yet they are quite serious factors in the life of the child. The normal child, who asks the mother to throw the baby out of the window, is prompted by the same forces which, in the child mentioned above with less favorable nervous balance, led to disturbing dreams of disaster to the brother.

A case illustrating the presence of the same forces at a still earlier age was that of T. A., the delicate son of a nervous mother. When he was 19 months old a baby brother was born; the patient appeared to be rather upset by this event; he was in bed for three days, and the physician thought he was jealous of the newcomer, "heart sick." "He didn't seem to want to walk," and for some time he required to be carried or taken in the go-cart; it was as if he demanded the attention which was given to the baby. His mood seemed to change, he was a little "distant" with his parents.

On several later occasions he showed evidence of the same trends; he wished that the baby were not there, he said that his mother did not love him, "you won't see me any more," "the dear God loves me."

In the third year of his life he had three "spells;" the first was elicited by his mother slapping him for obstinancy in refusing to lie down; the child held

his breath, became blue in the face. The second spell came on when, after clamoring insistently for something, he was scolded by his mother; he held his breath, became blue, appeared to lose consciousness. The third spell came on after he had been struck by his little brother. The child died in his fourth year from pellagra.

Here again there may be some reluctance to see in a child of these years evidence of complex factors which we are rather apt to consider of importance only at a more mature period. It is true that it is only at a later period that they come clearly into consciousness, and are apt to form clearly recognized motives. But it needs little maturity of intelligence to have a craving for affection, to be self-assertive, to demand affection of an exclusive nature; a child can feel in a very subtle manner, its intuitions are keen, and we have to remember that our life is determined not so much by intelligence as by those driving forces deeply rooted in the instiinctive life of the individual.

If one wish further illustration of the deep, underlying forces that sway the child's emotions, influence its reactions and are at the basis of many neurotic symptoms, there is available an extremely interesting presentation by Jung[1] of the conflicting forces in the nature of a girl of 4. The birth of a brother at that age proved to be a rather unsettling factor; the announcement of the probable arrival of the brother had already elicited the prompt answer, "then I would kill him." The problem introduced by this new factor into the situation of the child apparently led directly to the development of unusual moods, night terrors, ruminations, and some estrangement from the parents.

The fact that a child of 4 should have so much difficulty in assimilating a situation which many other children deal with in a very placid manner in itself gives one a measure of the nervous sensitiveness of the child. It is interesting, however, to note that before this very specific test was applied the child, who, it is true, was rather imaginative, had shown no evidence of nervous instability.

In paying so much attention to one factor in the life of the child, a factor it is true of cardinal importance, the aim has been to illustrate in some detail the important principle that neurotic symptoms may be the surface expression of complicated conflicts in the child's personality. No attempt has been made to sketch in all the main outlines of the child's life. There are many other problems before the child than those referred to; as he passes through the various stages of his evolution, he finds himself before succeeding problems of adaptation to an external regimen with regard to food and sleep and habits of the toilet, problems of adaptation to external restrictions as to his utter-

1. Jung, C. G.: Ueber Konflikte der kindlichen Seele, Jahrb. d. psychoan. u. psychopath. Forsch., 1910, ii, 33.

ances and behavior, of adaptation to the conflicting demands of the other self-assertive individuals who make up his world. With regard to each successive problem the child may show a constitutional difficulty of adaptation, a tendency to a neurotic persistence in the earlier phase; and each topic has its own familiar group of symptoms, which it would take us too far to review.

NEUROTIC UTILIZATION OF SYMPTOMS

So far we have discussed the origin of symptoms, and have emphasized the fact that symptoms may in some cases be the resultant of an internal conflict, a sort of compromise between the opposing forces in the patient's complex personality, an attempted solution of a strained situation in domestic politics.

We now pass over to the sphere of foreign politics, and consider the rôle which symptoms may play in enabling the child to dominate the environment. That rôle may be important to estimate if we wish to handle the situation judiciously. Symptoms may arise in various ways; they may be the result of a personal compromise, or they may be the expression of a nervous instability which needs no special conflict to elicit them, or they may even be the product of some casual somatic disorder; once they have arisen they may serve a certain function, and be made use of for the adaptation of the individual to the environment. Symptoms, whether of neurotic or other origin, are liable to be utilized by the neurotic child. In taking up the discussion of this topic, the endeavor again will be to exemplify in detail our conception in relation to a very limited number of symptoms, rather than to cover in a more general way a wide variety of symptoms.

Among the gastric symptoms presented by neurotic children vomiting is not uncommon and in some cases this symptom forms a very serviceable help to the child for the attainment of his ends. In both the following cases the neurotic symptoms of the child were fostered by the neurotic mother; what is laid at the door of heredity may often with more justice be attributed to the influence of the neurotic atmosphere supplied by the mother.

R. N., a boy of 17, was hardly able to read and write, but showed a surprisingly good reaction to the standard intelligence tests. His apparent backwardness was due to the almost complete neglect of school education, which was only partly justified by earlier sickness. His parents had tried on several occasions to send him to school; he then complained of headache and vomited when he was only a few yards from the house. The father one day insisted on the boy going to school, but the boy fell on the road as if in a faint, and was immediately rescued by the solicitous mother; from that date no further attempt at education was made and the boy remained in an exaggerated dependence on his mother, which pleased her very much. At 17 he used to climb on his mother's lap, and to say that he wanted to remain "mamma's baby," and that he did not want to grow up. The mother had

fostered in the child an attitude which was extremely strong in herself. She felt that a thread connected indissolubly the life of her mother, of herself, and of her child so that if one died the others would necessarily die. She said that evidently the child inherited his love for her; she herself had loved her parents so much that she cried for two years after she was married, until her parents came to live with her.

The neurotic parent is seldom willing to see her share of responsibility for the difficulties of the child; in order to understand the difficulties of the child, it would first of all be necessary to face honestly one's own difficulties and understand one's own life. Fortunately the mother was sufficiently cooperative for the boy's general hygiene to be put on a completely different basis; he made quick progress in his studies, but whether he will be successfully weaned is a very doubtful matter.

In another case where the situation was very similar, the vomiting had a more direct reference to dietary matters.

The patient, an only son of 9, was very capricious as to his diet, he would take only what he liked, and no more than he liked; he would accept milk only if flavored with coffee; as a rule he demanded steak for dinner. If his mother urged him to take more of some dish he would say, "I will vomit if you make me take another spoonful," and he kept his word.

Headache is another symptom which the child, as well as the adult, finds easily at his disposal in the face of unpleasant situations. It is frequently extremely difficult to determine how far we are dealing with headache of quite independent origin, or how far it is part of an unhygienic adaptation. The difficulty is increased when we are dealing with a girl subject to recurrent headache and gastric symptoms, whose mother is subject to megrim, a markedly hereditary disorder. It is extremely probable that in a certain number of such cases neurotic headache masquerades as inherited megrim.

Of the nervous manifestations of childhood, none are more alarming than the various attacks which are liable to occur. The diagnosis of epilepsy is often difficult and it is well to keep in mind the possibility that an attack, even though presenting some of the features of an epileptic equivalent, may really form part of a subtle mechanism by which the child attains a desired goal.

In the following case the rather complicated attacks seemed to express the dissatisfaction of the boy with his situation, and led to his getting the desired change, after which the attacks ceased.

G. J., a colored boy of 11, was referred from the Harriet Lane Home to the dispensary of the Phipps Clinic, May 28, 1915. The patient had been having very frequent "convulsions" since one day early in February, 1915, when he had been struck on the head by a baseball, without, however, being rendered unconscious. On the evening of the injury he was said to have vomited two long worms, and during the night he had several "convulsions." From that date he continued to have attacks several times a day; in these

attacks he behaved in a peculiar way, he used to bite, snap, froth, sing, run about and appear to converse with imaginary people, for example, his dead mother. He used finally to fall down. Before the attack his head felt heavy and dizzy, he felt as if he had to eat something; he did not remember his conduct during the attack, but said that after it he felt weak and drowsy.

These attacks might have been considered as atypical epileptic equivalents of traumatic origin; they appeared, however, to bear a striking relation to the situation. The boy was living in the country with his aunt and uncle and was very anxious to come into town; his attacks apparently made it very difficult for his aunt to keep him in the country. The boy himself put the matter very naïvely; "It's no wonder I'm having spells, I can't see much; nothing to keep my mind going; there's something to keep my mind going all the time in the city; if any one speaks rough to me it just seems if my head were coming off my shoulders; I want something to play with to keep my mind going; there's nothing to do but go out and play in the dirt." During the patient's stay in the Harriet Lane Home (April 2 to April 10, 1915), no convulsions were observed; the physical examination was practically negative. He was readmitted to the hospital on April 26, 1915, as the attacks had reappeared on his return to the country. No convulsions were observed in the hospital. Arrangements were made for the boy to live with his father in the city and since being in the city the attacks have ceased.

The exact origin and nature of these attacks may be difficult to explain, but there seems to be no doubt that they were utilized by the child for his own purposes to obtain a desired result; how far such utilization is subconscious or how far there may be some deliberate cultivation of the attacks is difficult to determine.

In the following case there was not the same obvious gain derived from the symptoms:

B. M., a colored boy of 10, was referred to the dispensary of the Phipps Psychiatric Clinic from the Harriet Lane Home on Oct. 25, 1915. After a normal infancy he began at the age of 3 years to have, once or twice a year, "spells of weakness" lasting for a few minutes. These were described as a "limpness of the body giving way." "You could tell the spell was coming on, he would get quite limp, and would fall, he would groan for a few minutes and then get up." During the earlier attacks he would attempt to answer questions, and would complain of feeling bad. In the later attacks there was more difficulty in answering questions. For the past two years he had about three or four attacks a year; there never was a preliminary cry, he never hurt himself in falling, he never wet or soiled himself during the attacks. Sept. 14, 1914, he had an attack in which he fell in a field; he was carried into the house and placed in bed, where he groaned and moved about uneasily for about ten hours. During the winter he had two attacks.

In September, 1915, his mother at breakfast said that she was feeling bad; he said, "I feel bad too, my head feels numb and dead." After breakfast his mother told him and his sister to wash the dishes; he said he couldn't as he had pains in the stomach. When his mother insisted, he went into another room, lay down on the lounge, and ten minutes later was found on the floor rolling as if in agony; he fought his father off, and could not respond clearly to questions. For two days he continued in perpetual motion, rolling in his bed and crawling out of it. He talked of wanting to go on a blue train, he clamored to go to Columbia. He slept well at night; in the morning he resumed his thrashing around, but would pause when spoken to. He knew his father, but for several days did not seem to know his mother or the other members of the family. This "violent state" lasted for eight or ten days, after which he became quiet, although he still talked in a "flighty" way.

Apart from these episodes the boy had shown no evidence of nervous instability; he gave no trouble as to his food or sleep, there was no bed-wetting or night-terrors. In his relationship to the other members of the family he had shown no specially intense attachments.

The child had been accustomed from the age of 3 or 4 years to go once a year to camp-meeting; he himself was a "great preacher round home," he would perform before other children with much unction and was applauded for his imitations of the convulsive movements of the ecstatic.

Although nothing in the situation seemed to explain the attacks, the boy's obvious desire to impress his comrades and the prestige derived from his own peculiar attacks seemed to have much to do with their origin; and the development of an attack in face of an unpleasant task seemed to favor this conception of the disorder.

The utilization of symptoms in a neurotic manner can not be more clearly exemplified than in the contrast between the two following cases, in which the symptoms consisted of involuntary movements. In one case we see the way in which a symptom, casually occurring in a child of good constitution, and correctly treated by the environment, passes without leaving a trace; while in the other case a similar symptom, perhaps of equally casual origin, is made use of by the neurotic individual and elaborated into a rather striking clinical phenomenon.

In the first case we have an experience, described by Scholz,[2] which happened to himself when he was 10 years old. One day just before the writing lesson his right hand began to tremble, he could only make illegible scrawls, and with a certain pride he demonstrated the symptom to the teacher. The latter paid no attention to it, a little to the boy's chagrin, and his father, a physician, treated the matter as of no interest. The tremor never reappeared.

Contrast this with the following case of a school girl reported by Jung:[3]

In the second year of school in the writing class, which she disliked, her right hand began to twitch; soon she was unable to write, and had to give up the class. The involuntary movements spread and became general, a "hysterical chorea;" owing to these symptoms and to morbid fears her attendance at school was very irregular and at 12 was completely discontinued. On the onset of menstruation at the age of 15 the involuntary movements abruptly ceased, and were now replaced by a variety of other hysterical symptoms.

Here we see how a girl of poor nervous balance, which showed itself later in a variety of hysterical symptoms, had at an early age utilized apparently involuntary movements for a definite end. When the patient looked back on this period she realized that she had culti-

2. Scholz, L.: Anomale Kinder, p. 152.
3. Jung, C. G.: Diagnostische Assoziationstudien, ii, 31.

vated the disorder; she admitted that she could have controlled the movements if she had exerted herself and that it suited her to be sick.

It is probable that in some cases the relapses after a Sydenham's chorea represent, not a return of the previous condition, but the neurotic utilization of symptoms which the previous sickness has made familiar.[4]

ORIGIN OF NEUROTIC SYMPTOMS IN GENERAL

So far we have discussed two main topics. The first related to the fact that familiar symptoms may be the indicators of conflicts in the child's life, the presence of which is often not suspected; the recognition of these conflicts is important for the treatment of the child. The second topic was the way in which various symptoms, no matter what their origin, may be utilized by the neurotic child; it is necessary to recognize the circumstances which tend to foster the symptoms, if the situation is to be put on a hygienic basis. If the symptoms are utilized in the adaptation of the child to its environment, it is not meant thereby that the child does so clearly and deliberately; we are dealing with a biological adaptation in which conscious purposes may play a very subordinate, even a vanishing, rôle.

A third topic remains for discussion, namely, the origin and nature of neurotic symptoms in general, quite apart from their later utilization or the conflicts which in some cases they may indicate. The fact that a symptom may in some cases be utilized in a certain way, and may indicate personal conflicts, does not entitle us to conclude that in every case it is so utilized, and that it must always indicate such conflicts. There may be other cases in which the same symptoms are elicited by a great variety of causes as the expression of a constitutional instability. They would then be a measure of the nervous stability of the child, and their practical importance would consist in the indication that the child with such symptoms may not be able to meet the same stress and strain as his fellows, and may require certain special safeguards.

One of the earliest of such symptoms is that the infant is extremely easily startled; disorders of sleep may also be pronounced at an early age; other symptoms are an exaggerated conservatism with regard to diet, the refusal to be weaned and to make the regular progress up the dietary ladder; anomalies as to micturition and defecation may be met with; the child may show apparently capricious but determined refusal to pass water or to have movements at suitable times, and an apparent constipation may represent an early form of self-assertion, which may yield to coaxing or a whipping; vomiting, headache, chorei-

4. Thiemich, M., and Zappert, J.: Die Krankheiten des Nervensystems im Kindesalter, p. 193.

form movements, stammering, tics, and habit-movements have to be considered; while a great variety of attacks may occur varying in severity from the familiar tantrum of temper to epileptiform convulsions.

This list of symptoms is by no means complete and each symptom presents many special problems. Here again only a very few symptoms will be discussed.

As to the disorders of sleep, reference has already been made to the complex determinants which may be at the basis of some cases of sleeplessness. The night-terror (pavor nocturnus) so frequent in children may occur in a very complex setting as in the case of the 7-year-old boy described above and in the 4-year-old girl described by Jung. But it is important to recognize that night-terrors may arise in a very simple setting and may not indicate more than a vague nervous tension which we have difficulty in analyzing further. Thus Miss Shinn,[5] in her charming description of the development of her niece, notes at the end of the fourth month an early indication of this phenomenon, and a still more definite episode at the seventh month. In some cases overstimulation before bedtime, especially emotional stimulation, such as is supplied by moving pictures, seems to be responsible for the symptom. Strohmeyer[6] calls attention to the fact that in some cases the symptom is related to the nascent sexual instinct, which may be partly aroused by overcaressing and carelessness with regard to the sleeping arrangements. While the night-terror is as a rule a benign symptom, it may have a more dread significance, it may be an epileptic equivalent. This is considered by Aschaffenburg[7] to be probable if the symptoms are accompanied by bed-wetting and if the child remains dull and confused for more than a few minutes, notwithstanding efforts to arouse him. Thiemich,[8] however, lays no such stress on a much longer period of confusion and considers the connection with epilepsy extremely rare.

In the following case the symptoms seemed to be partly related to a very emotional experience which the imaginative child had undergone:

J. S., a boy of 8, Feb. 6, 1915, was referred from the Harriet Lane Home to the dispensary of the Phipps Psychiatric Clinic on account of night-terrors. The patient would wake up in a panic and for a period of fifteen or twenty minutes or longer would see imaginary animals and talk in distress about frogs, turning wheels, cannibals, etc.; the symptoms had begun at the age of 6; in the earlier attacks he would, after coming to himself, pass urine and

5. Shinn, M. W.: The Biography of a Baby, p. 195.
6. Strohmeyer, W.: Vorlesungen über die Psychopathologie des Kindesalters, p. 25.
7. Aschaffenburg, G.: Der Schlaf im Kindesalter und seine Stoerungen, p. 20.
8. Thiemich, M., and Zappert, J.: Footnote 4, p. 219.

go off to sleep. Of late the boy had wet the bed during these attacks; and, in addition to the night-terrors, he would occasionally in the afternoon become pale, and speak incoherently for fifteen to twenty minutes, referring to peculiar shadows or figures which he saw.

The boy had shown no nervous symptoms until the age of 6. At that age the mother wished to punish him, but thought a whipping would have little effect; she therefore put him down in the cellar, where she assured him the rats would eat him. He was much upset and owing to his screaming he was released in two minutes; he played about for an hour and then fell asleep. On waking from his sleep he started to scream, said that he saw rats and frogs and people. From that time the boy was troubled with bad dreams, in some of which he dreamed of rats. When he was asked whether any incident had ever occurred to make him dream of rats, he made no reference to the above episode. He tended to weave any recent dramatic experience into his dreams, which were peopled with the heroes of the moving pictures. The boy was of an unusually imaginative disposition, he was already a poet, and this trait may explain the quasihallucinatory phantasies in the daytime. Thus, he made reference to an imaginary boy smiling at him and to rather mysterious "chills" or clouds of smoke, which he saw or conjured up. "I think I see them a little now, chills, clouds of smoke . . . when I think of them, I can hardly forget it . . . it seems just like clouds of smoke, I don't really see them but I think of them and that makes me a little bit just like I see them. . . . I hollered out to mamma to stop them people, they were stealing the smoke . . ."

These utterances were rather a contrast with the frank, healthy appearance of the red-cheeked urchin; as a matter of fact, two weeks later the boy was already sleeping very much better, and the bad dreams and fantastic "chills" have been practically absent since that time. One further trait of the boy may be mentioned; in kissing his mother he had a habit of biting her. "I try to kiss but I can't; I just bite a little bit; I can't help it." He would kiss his little sister, however, without biting her. Notwithstanding the hallucinatory confusion, the bed-wetting, the afternoon attacks, in this case it is doubtful whether epilepsy has to be seriously considered.

An emotional episode seemed to precipitate the symptoms and to give them a certain color, but a similar picture can develop with no such apparent cause and we are bound to lay the stress on the constitutional nervous instability of the patient.

Bed-wetting (enuresis nocturna) is another very common sign of nervous instability. In some cases it is the response to a rather complicated situation, as in the case of a boy of 5 who showed marked increase of bed-wetting, occasional soiling and night-terrors, when removed from his mother and placed in an orphanage; when placed again with his mother the condition showed immediate improvement. The frequent connection of bed-wetting with masturbation is noted by Strohmeyer.[9] In many cases, however, there is no trace of any of the above factors, and the symptom has merely the value of a neurotic indicator.

The vomiting of neurotic children may arise on the same general basis of neurotic instability; thus in the cyclic vomiting of children the symptom may develop where no special conflict can be discovered, and

9. Strohmeyer, W.: Footnote 6, p. 55.

the symptom seems to form part of no neurotic adaptation. It is not necessary to assume that the mechanism of the symptom is always as complex as in the cases reported above of the neurotic utilization of the symptom, or in cases such as that of Strohmeyer, in which the vomiting ceased after the child had talked over his masturbation with the physician and received reassurances from him.

Choreiform movements may represent the hysterical expression of repressed factors, and may be utilized in a neurotic way, as in the case of Jung, referred to above. In a great many cases choreiform movements seem to play a much less definite rôle and to have an explanation at a simpler biological level. They occur in a large number of children who show evidence of general constitutional inferiority, and they may represent a special type of motor inferiority going parallel with the inferiority which is present in the intellectual and the emotional life. Choreiform movements need not be associated with mental defect, but may simply be the indication of a rather special type of nervous instability.

Among the indicators of nervous instability sexual activities have attracted much attention. The exact rôle which the sexual instinct plays in the development of nervous manifestations in the child and in the adult is a subject of much debate, often rather acrimonious; the tendency undoubtedly in the past has been for us to overlook many of its manifestations, influenced by the altogether too simple conventional conception of the life of the child. Before considering, however, various symptoms as secondary to sexual activities, we have to recognize that the precocious development of these interests and activities and a disproportionate prominence of certain elements in these complicated functions are in themselves evidence of a neurotic instability, except in cases in which unfortunate external circumstances have forced the development of instinct. Thus precocious and excessive masturbation has to be looked on as evidence of nervous instability, as a symptom, and not only as a cause, of nervousness; and, in estimating the further nervous symptoms of the individual child, it may be difficult to know how far these are directly related to the sexual activities, or how far they draw their origin from a common source, from the underlying constitutional instability. It is extremely important that these factors should be estimated at their correct biologic value, and dealt with according to sound hygienic principles and not according to narrow inappropriate ethical standards. An open and healthy atmosphere will perhaps spare the neurotic child the development of methods of adaptation which may handicap the whole of the adult life.

A separate chapter would be required for a discussion of the various attacks which occur in nervous children. The exact relationship of many of these attacks to spasmophilia on the one hand and to epilepsy on the other is a problem of very great importance. In the individual case it may be difficult to draw the line between tantrums of temper in a neurotic child and spasmophilic attacks. Nor is it clear how far we should include under spasmophilia all those episodes in neurotic children, precipitated by definite emotional causes which we are not entitled to refer either to hysteria or to epilepsy, episodes to which Bratz[10] has given the name of *affektepileptische Anfälle,* and which are referred to under a great variety of names by other authors. Among these attacks may be instanced Wegbleiben (as in the case of T. A.), narcoplepsy, attacks of vertigo and fainting, and attacks similar to petit mal and grand mal.

Further work on these disorders may enable us in a certain number of cases to formulate the constitutional inferiority of the individual in definite biochemic and physiologic terms, and may reduce considerably the number of those cases in which we are still forced to employ such general terms as constitutional nervous instability or neuropathic constitution. If in the preceding part of our paper we have emphasized the importance of the wider psychobiologic attitude for the proper understanding of neurotic symptoms, in the present sphere we are dependent on the researches of the pediatrist, employing biochemic and physiologic methods.

SUMMARY

The study of the psychoneuroses of the adult has thrown a good deal of light on the complexity of the life of the child; conflicts analogous to those of the adult are present in childhood, and may give rise to the same types of nervous disorder. The neurotic child may show at an early age difficulty in passing from one stage of adaptation to another, a tendency to retain the attitude of the earlier stage, an incomplete assimilation of the more mature attitude.

Familiar symptoms may indicate the presence of such a difficulty in the child's adaptation and the recognition and treatment of the difficulty will depend on a just appreciation of the complexity of the child's life, a complexity which is alien to the conventional conceptions of childhood.

In the study of the rôle played by certain symptoms in childhood it is useful to remember that these symptoms may be a method by which the child, more or less subconsciously, asserts himself and enjoys certain immunities or privileges.

10. Bratz, Emil: Die affektepileptischen Anfälle der Neuropathen und Psychopathen, Monatschr. f. Psychiat. u. Neurol., 1900, xxix, 45, 162.

Although certain symptoms may arise in a very complex manner and persist owing to their utility, they need not have such complex significance; they may, as the indicators of a constitutional nervous instability, be elicited by a great variety of causes. The pediatrist, by the application of accurate methods to the study of these early symptoms, may contribute to psychopathology a much clearer formulation of the basis of some types of nervous constitution.

I take this opportunity of thanking Dr. Howland for his help in the preparation of this paper, and for placing at my disposal the pediatric records of several of the cases referred to.

THE EFFECT OF COLD AIR ON THE BLOOD PRESSURE IN PNEUMONIA IN CHILDHOOD*

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Largely as the result of the enthusiastic endorsement of Northrup[1] of New York in a series of papers on the subject, published between 1904 and 1906, the cold-air treatment of pneumonia has been more or less completely adopted by most pediatricians and by many practitioners. No very satisfactory explanation for the supposedly beneficial results of this method of treatment was advanced, however, in the beginning.

Howland and Hoobler,[2] writing in 1912, stated that it was apparent that children seriously ill with pneumonia might have a blood pressure somewhat below what might be expected at their age, and that the symptoms of the death of children from pneumonia were those of vasomotor failure. They found that the effect of cold, fresh air in patients with active pneumonia was always to produce a rise in blood pressure. Removal to a warm (65 F.) room produced a fall in blood pressure. The results were absent or much less striking in convalescents. They were unable to get any results by putting children out of doors in warm weather. They concluded, therefore, that the all-important factor in the out-of-door treatment was cold, and that the rise in blood pressure was brought about by a reflex stimulation of the vasomotor center by the action of the cold air on the skin. They also stated that there is no doubt that an increase in the blood pressure, when it is abnormally low, which is constant and continuous and which is brought about without exhaustion or bad effects, is of the greatest value. This explanation of the beneficial effects of the outdoor treatment was generally accepted.

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1. Northrup: Med. News, 1904, lxxxiv, 823; Chicago Med. Recorder, 1904, xxvi, 628; Med. Rec., New York, 1905, lxvii, 253; Boston Med. and Surg. Jour., 1906, cliv, 216; Jour. Am. Med. Assn., 1906, xlvii, 1182; Med. Jour., New York, 1907, lxxxvi, 12.
2. Howland and Hoobler: Am. Jour. Dis. Child., 1912, iii, 294.

About this time, however, Weigert[3] published a paper in which he concluded, on the basis of his experience and from his study of the literature, that no rule can be established for the blood pressure in pneumonia, and that in consequence blood pressure readings are of no prognostic value. Newburgh and Minot,[4] in 1914, from a study of a considerable number of cases, mostly in adults, found that the systolic pressure in the fatal cases was continuously above the systolic pressure in the persons who recovered. They concluded, therefore, that failure of the peripheral circulation cannot be a common cause of death in pneumonia. Porter and Newburgh[5] have also recently shown experimentally that the vasomotor center is not impaired in fatal pneumonia in animals.

Freeman[6] states, moreover, that Schloss, in work done under his supervision at the New York Foundling Hospital and at the New York Nursery and Child's Hospital, was unable to corroborate Howland and Hoobler's results, and that Hartshorn has carried out a considerable series of blood pressure experiments at the Roosevelt Hospital with no constant results. They found that while some children showed a considerable increase in blood pressure on being put out of doors, others showed no increase, while, on the other hand, there was no constant fall of blood pressure noted when the children returned to the ward. In fact, the blood pressure was no higher out of doors than in the ward.

Not being aware of the investigations of Freeman and his co-workers and having been struck with the fact that the results of Weigert, Newburgh and Minot, and Porter and Newburgh did not confirm those of Howland and Hoobler, the writers made a study of the effect of cold, out-of-door air on the blood pressure in pneumonia in childhood, at the Boston Children's Hospital during the past winter. There were made 387 observations on thirty-two children. The ages of these children varied between 2 and 10 years, nineteen of them being under 5 years of age.

Eight of the children died. The illness was classified as very severe in three, severe in fourteen, moderately severe in four and mild in three.

The methods employed in the investigation were as follows: The children were kept in the warm ward for a varying number of hours. They were then put out of doors for a varying number of hours, brought back into the ward again, put out again, and so on, until after the crisis occurred or the child died. The blood pressures were taken at the end of each period, that is, just before going out of doors when the child had been in the ward for some hours, and just before coming

3. Weigert: Samml. klin. Vort., 1911, 459.
4. Newburgh and Minot: Arch. Int. Med., 1914, xiv, 48.
5. Porter and Newburgh: Am. Jour. Physiol., 1914, xxxv, 1.
6. Freeman: Am. Jour. Med. Sc., 1916, cli, 1.

into the ward after it had been out of doors for some hours. The Tycos sphygmomanometer was the instrument employed. The width of the cuff was four and one-half inches. Except in a few instances the right arm was always used for taking the pressures. The readings of the blood pressures were made at the ends of the second and third phases, that is, after the pulse was obliterated (first phase) the systolic reading was made at the first hard thump following the few dull thumps of the second phase. The diastolic reading was made at the end of the third phase, at the time when the definite change from the hard thump to the dull thump of the fourth phase occurs.

The protocols give the data in each case in detail. The temperature readings are in the Fahrenheit scale. "Ent." means at entrance. "In" means that the readings were taken at the end of the time spent in the ward, and "out" that they were taken just before the child was taken in from being out of doors.

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6528	3	In	Ent.*	72	130	40	100	65	35
Age, 2½ years		Out	2	50	125	35	98	60	38
Left lower lobe,		In	2	70	130	40	103	67	36
severe		Out	2	50	120	30	100	65	35
		In	1	74	115	35	102	64	38
		Out	1	54	110	30	100	65	35
	4	Out	12	52	120	40	105	70	35
		In	1	68	110	35	110	75	35
		Out	1	54	115	40	105	70	35
		In	1	72	115	40	105	68	37
		Out	1	54	130	38	104	70	34
		In	3	70	125	40	100	65	35
		Out	3	50	120	35	110	75	35
	5	Out	15	60	140	40	118	80	38
		In	1	72	137	38	115	75	40
		Out	2	50	145	40	118	78	40
		In	2	82	150	45	106	63	43
		Out	2	48	160	50	105	60	45
		In	2	76	130	45	105	60	45
	6	Out	12	54	115	30	108	70	38
		In	1	68	115	30	105	65	40
		Out	2	52	120	30	100	60	40
		In	2	78	118	32	105	65	40
		Out	2	52	115	30	104	64	40
		In	1	78	130	42	100	60	40
		Out	2	52	135	45	104	63	40
	7	Out	14	50	120	32	102	58	44†
		In	2	72	115	30	102	56	46

* Ent. means at entrance. The temperature readings are in the Fahrenheit scale. The tycos sphygmomanometer was used with a four and a half inch cuff. All blood pressures were taken at end of periods In or Out, or in other words, just before changing from warm to cold, or vice versa. Except in a few instances, the right arm was used for all pressures. Blood pressure readings were made at the ends of the second and the third phases, that is, after the pulse is obliterated (first phase) the systolic reading is made at the first hard thump following the few dull thumps of the second phase. The diastolic reading is made at the end of the third phase or where there is a perceptible drop from the hard thump to the dull thump of the fourth phase.

† Crisis.

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6546 Age, 6½ years Left lower lobe, mod. severe	4	In	Ent.	70	135	43	85	60	25
		Out	2	45	130	45	95	55	45
		In	3	75	120	32	98	55	43
		Out	2	42	118	30	95	50	45
	5	Out	14	40	80	25	95	45	50†
		In	3	70	100	23	100	55	45
No. 6559 Age, 7 years Left lower lobe, severe	5	In	Ent.	70	105	48	98	60	38
		Out	2	40	120	38	105	55	50
		In	2	70	120	42	108	60	48
		Out	2	42	90	42	108	58	50
	6	Out	14	36	90	25	95	53	42†
No. 6629 Age, 3 years Right upper lobe, very severe	4	In	Ent.	70	128	40	113	85	28
		Out	2	42	120	40	100	60	40
		In	3	70	132	35	100	65	35
		Out	3	40	128	35	98	60	38
	5	Out	15	38	128	40	98	60	38
		In	2	70	120	35	95	55	40
		Out	3	50	128	35	95	55	40
		In	4	70	132	38	88	50	38
	6	Out	12	40	130	40	90	52	38
		In	4	65	120	36	92	54	38
		Out	4	50	118	34	92	55	37
		In	2	70	120	40	90	52	38
	7	Out	12	45	130	35	88	50	38
		In	4	70	135	40	90	54	36
		Out	4	45	130	38	82	45	37
		In	3	70	140	42	85	45	40
	8	Out	12	45	100	35	75	40	35†
		In	12	65	110	32	90	50	40
No. 6611 Age, 7 years Right lower lobe severe	7	In	Ent.	70	160	40	95	50	45
		Out	3	40	120	55	85	55	30
	8	Out	15	40	110	30	80	40	40
		In	2	70	120	42	78	40	38
		Out	4	42	130	40	80	40	40
		In	4	65	130	50	82	42	40
	9	Out	12	38	120	36	80	40	40
No. 6614 Age, 2¼ years Left lower lobe, mild	3	In	Ent.	70	162	38	80	40	40
		Ont	3	40	150	40	75	38	37
	4	Out	15	40	130	36	83	40	43†
		In	4	62	110	32	82	42	40

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6435	7	In	Ent.	70	165	38	95	70	25
Age, 3 years		Out	2	40	150	38	95	65	30
Right and left lower lobes, very severe	8	Out	14	34	132	40	93	58	35
		In	2	68	138	43	92	55	37
		Out	3	42	150	32	95	55	40
		In	3	70	160	40	80	60	20
		Out	3	42	168	42	78	50	28
		In	4	64	180	48	85	50	35
	9	Out	12	40	165	43	85	50	35
		In	2	70	162	40	88	60	28
		Out	3	50	160	52	88	62	26
		In	2	70	180	55	82	54	28
		Out	2	50	180	55	78	?	?
		Patient died several hours later, no blood pressure obtainable shortly before death (stimulation)							
No. 6628	2	In	Ent.	65	120	37	100	70	30
Age, 8 years	3	Out	12	40	130	48	100	50	50
Left lower lobe, mod. severe		In	2	70	120	30	98	55	43
		Out	2	45	120	30	95	50	45
		In	4	72	130	30	98	48	50
		Out	3	40	125	28	95	55	40
	4	Out	15	40	132	43	88	48	40
		In	2	70	130	45	90	52	38
		Out	2	45	128	40	85	42	43
		Out	5	38	132	42	88	47	38
		In	4	70	120	48	90	45	45
	5	Out	12	35	98	32	90	50	40
		In	2	70	112	40	88	52	36
		Out	4	35	110	38	94	60	34
		In	3	70	100	40	85	50	35
		Out	2	40	85	30	80	50	30‡
	6	Out	14	40	70	23	84	50	34
		In	2	70	75	25	82	50	32
No. 6563	2	In	Ent.	70	120	48	125	80	45
Age, 5½ years		Out	2	40	130	45	120	80	40
Left lower lobe, mod. severe	3	Out	14	36	140	48	118	78	40
		In	2	70	140	42	118	75	43
		Out	2	40	142	38	115	75	40
		In	2	68	110	40	118	78	40
		Out	3	42	115	35	122	80	42
		In	2	72	122	36	124	80	44
	4	Out	12	40	112	38	115	70	45
		In	2	68	128	40	113	70	43
		Out	3	40	140	40	125	80	45
		In	5	70	143	48	120	80	40
	5	Out	12	40	105	32	128	82	46
		In	2	70	110	30	118	80	38

‡ Lysis.

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6427 Age, 3½ years Left lower lobe, severe	2	In	Ent.	70	130	40	100	60	40
		Out	4	40	135	42	84	60	24
		In	2	70	142	55	86	58	28
	3	Out	12	40	132	40	94	55	39
		In	2	68	134	38	92	56	36
		Out	2	38	130	34	92	54	38
		In	3	72	120	30	90	50	40
		Out	3	40	126	34	92	55	37
	4	Out	15	40	132	40	96	50	46
		In	4	72	132	45	95	48	47
	5	Out	12	45	132	40	100	58	42
		In	2	70	138	46	94	50	44
		Out	2	42	132	42	92	54	38
		In	5	70	128	38	88	44	44
		Out	2	40	130	42	90	48	42
	6	Out	14	38	108	40	104	60	44
		In	3	70	115	38	98	55	43
		Out	4	45	120	40	95	55	40
		In	3	72	128	43	92	50	42
		Out	2	50	135	47	90	50	40
		Out	14	45	108	35	88	55	33†
No. 6547 Age, 4 years Left lower lobe, very severe	13	In	Ent.	65	175	68	85	40	45
		Out	2	40	190	80	82	48	34
		Died two hours later (stimulation)							
No. 6535 Age, 10 years Right upper lobe, severe	2	In	Ent.	70	160	45	108	80	28
		Out	3	35	150	42	95	65	30
		In	3	70	150	42	92	72	22
		Out	2	38	...	..	90	50	40
	3	Out	14	35	162	40	90	60	30
		In	2	70	...	..	100	70	30
		Out	4	42	150	50	75	50	25
		In	2	72	190	62	78	50	28
		Died one hour later (stimulation)							
No. 6620 Age, 5 years Whole right lung	10	In	Ent.	65	160	40	90	50	40
		Died two hours later (stimulation)							
No. 6561 Age, 6 years Both lower lobes	6	In	Ent.	70	128	38	135	110	25
		Died one hour later (stimulation)							
No. 5965 Age, 5 years Right upper lobe	2	In	Ent.	72	130	67	98	46	52
	3	Out	12	42	140	82	65	30	35
		Died less than an hour later (stimulation)							

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6678	7	In	Ent.	68	180	60	75	45	30
Age, 3 years	8	Out	12	15	150	60	72	50	22
Right upper lobe, severe		In	4	70	152	56	90	60	30
		Out	4	25	142	48	82	50	32
		In	3	70	120	55	88	60	28
	9	Out	12	20	148	60	82	56	26
		In	3	70	140	58	86	52	34
		Out	5	38	145	52	82	54	28
		In	4	69	150	60	90	60	30
	10	Out	12	15	132	48	84	56	28
		In	4	70	138	49	84	54	30
		Out	4	38	134	42	80	52	28
		In	2	65	148	60	82	50	32
		Out	2	27	142	50	82	52	30
	11	Out	14	20	120	37	80	52	28
		In	4	70	118	35	86	58	28
		Out	3	25	120	35	88	60	28
		In	3	68	120	32	90	54	36
	12	Out	12	10	120	30	72	40	32†
No. 6650	3	In	Ent.	65	124	40	85	45	40
Age, 2 years		Out	4	50	158	32	110	58	52
Left lower lobe, severe		In	4	70	120	43	110	60	50
	4	Out	12	38	140	44	98	58	40
		In	4	60	140	42	98	56	42
		Out	2	35	124	42	96	54	42
		In	2	65	148	34	100	62	38
		Out	2	40	120	32	102	60	42
		In	1	70	132	40	105	58	47
	5	Out	12	35	120	35	96	50	46
		In	4	68	110	28	90	48	42
		Out	4	28	120	36	88	54	34
		In	3	70	140	40	98	62	36
	6	Out	12	35	100	35	85	50	35†
No. 6586	8	In	Ent.	65	145	33	85	50	35
Age, 8 years		Out	3	45	132	32	82	50	32
Right upper lobe, severe		In	2	60	120	30	85	48	37
	9	Out	12	42	132	30	78	45	33
		In	4	70	125	34	85	48	37
		Out	2	45	125	34	87	50	37
		In	3	70	120	28	90	45	45
	10	Out	12	45	108	30	80	50	30
		In	3	70	105	28	80	40	40
		Out	3	45	115	28	82	42	40
		In	3	72	120	40	80	40	40
		Out	2	45	108	25	82	44	38
	11	Out	14	40	105	25	78	50	28‡
		In	4	65	120	28	78	45	33
		In	10	68	125	24	75	40	35
No. 6493	?	In	Ent.	70	120	32	95	48	47
Age, 3½ years		Out	12	45	180	52	100	50	50
Left lower lobe, very severe		Death two hours later (stimulation)							

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6591	4	In	Ent.	65	155	40	95	50	45
Age, 4 years	5	Out	12	40	140	38	92	50	42
Whole left lung, very severe		In	2	72	...	..	92	48	44
		Out	3	45	...	..	90	50	40
		In	3	70	175	48	92	54	38
		Out	2	38	...	..	90	55	35
		In	3	70	...	..	90	50	40
	6	Out	12	38	120	40	92	60	32
		In	2	70	...	..	90	62	28
		Out	4	35	...	..	90	60	30
		In	3	72	132	55	85	48	37
	7	Out	12	38	132	37	92	55	37
		In	2	70	...	..	95	60	35
		Out	2	40	...	..	92	58	34
		In	2	68	140	40	90	56	34
		Out	2	40	...	..	90	55	35
	8	Out	14	38	142	37	88	52	36
		In	2	70	...	..	90	50	40
		Out	2	40	...	..	88	52	36
		In	3	70	168	37	90	54	36
		Out	3	40	...	..	90	52	38
	9	Out	15	35	145	37	82	40	42
		In	4	70	172	60	84	45	39
		Out	6	50	...	..	82	42	40
	10	Out	18	42	142	60	80	42	38
		In	2	65	...	..	84	52	32
		Out	2	40	...	..	92	60	32
		In	5	70	155	60	90	54	36
		Out	2	40	...	..	90	54	36
	11	Out	14	36	145	60	95	50	45
		In	3	70	...	..	95	52	43
		Out	3	45	...	..	92	52	40
		In	3	72	152	58	92	50	42
		Out	2	50	...	..	92	55	37
	12	Out	14	42	120	40	90	52	38‡
		In	4	68	125	45	86	48	37
No. 6607	4	In	Ent.	70	162	52	100	56	44
Age, 3½ years		Out	2	25	130	40	85	45	40
Left lower lobe, mild	5	Out	12	28	130	35	80	45	35†
No. 6601	4	In	Ent.	68	130	48	72	40	32
Age, 4 years									
Left lower lobe, mild	5	Out	12	35	130	28	76	40	36†
No. 6670	5	In	Ent.	70	132	45	88	56	32
Age, 5½ years		Out	2	28	...	..	88	58	30
Right upper lobe, severe		In	2	70	125	42	88	60	28
	6	Out	12	28	100	32	88	58	30
		In	4	65	120	48	90	56	34
		Out	4	30	...	..	86	52	34
	7	Out	12	30	100	32	80	48	32†

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6740	8	In	Ent.	70	120	32	82	50	32
Age, 2½ years	9	Out	12	20	175	60	102	60	42
Both lower lobes, very severe		In	5	60	200	80	84	50	34
		Out	4	30	160	60	80	40	40
		In	5	54	165	80	84	35	49
		Death several hours later (stimulation)							
No. 6693	4	In	Ent.	70	142	60	105	60	45
Age, 3½ years	5	Out	12	40	135	62	92	50	42
Right upper lobe, very severe		In	4	75	...	..	105	65	40
		Out	4	35	...	..	108	65	43
		In	3	72	148	52	118	65	53
	6	Out	12	30	135	48	94	50	44
		In	4	70	158	60	98	56	42
		Out	4	38	...	..	90	50	40
		In	2	70	155	55	94	55	39
		Out	2	35	150	53	90	50	40
	7	Out	14	32	120	34	90	56	34
		In	4	72	112	43	94	50	44
		Out	4	38	115	40	100	54	46
		In	3	72	110	35	102	48	54
	8	Out	12	24	120	37	85	45	40†
No. 6749	3	In	Ent.	72	155	32	84	48	32
Age, 2 years		Out	2	35	150	38	80	52	28
Left lower lobe, severe		In	2	70	150	45	84	50	34
	4	Out	12	30	140	52	90	60	30
		In	4	70	135	55	90	56	34
		Out	4	30	138	60	84	50	34
		In	3	68	135	50	78	42	36
	5	Out	12	30	128	35	80	45	35†
No. 6760	4	In	Ent.	72	158	53	74	42	32
Age, 4 years		Out	4	35	140	57	78	40	38
Right lower lobe, severe		In	4	72	132	48	78	42	36
	5	Out	12	32	112	40	80	46	34
		In	4	70	128	43	96	54	42
		Out	3	35	180	60	100	48	52
		In	3	68	148	50	90	45	45
	6	Out	12	32	125	48	90	54	36
		In	4	72	125	48	75	38	37
		Out	3	34	120	48	74	42	32
		In	4	72	162	60	70	40	30
	7	Out	12	28	135	60	82	50	32
		In	4	70	120	48	78	46	32
		Out	4	35	122	48	78	44	34
		In	4	68	132	52	78	40	38
	8	Out	12	28	130	32	76	44	32†

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 6787 Age, 2¾ years Left lower lobe, severe	3	In	Ent.	68	135	60	82	54	28
	4	Out	12	40	120	40	76	52	24
		In	4	70	...	..	74	54	20
		Out	3	45	...	..	74	56	18
		In	3	70	120	37	76	56	20
	5	Out	12	40	142	52	72	54	18
		In	4	72	...	..	72	43	29
		Out	4	42	...	..	70	45	25
		In	4	70	144	48	70	45	25
	6	Out	12	40	144	48	68	42	25
		In	4	78	...	..	70	38	32
		Out	4	45	...	..	72	38	34
		In	4	72	130	43	72	39	33
	7	Out	12	40	130	40	68	40	28
		In	4	72	...	..	74	42	32
		Out	4	40	...	..	72	40	32
		In	4	70	122	38	72	42	30†
		Out	12	40	108	32	70	38	32
No 6797 Age, 3½ years Right lower lobe, severe	2	In	Ent.	65	142	60	68	40	28
		Out	4	50	...	..	72	45	27
		In	4	70	168	68	70	42	28
		Out	2	50	...	..	70	44	26
		In	2	70	...	..	69	42	27
	3	Out	12	42	142	64	68	40	28
		In	4	72	...	..	68	35	33
		Out	4	50	...	..	78	56	22
		In	4	70	158	80	94	64	30
	4	Out	12	45	145	62	88	60	28
		In	4	70	140	58	84	60	24
		Out	4	50	...	..	86	64	22
		In	4	70	145	54	88	63	25
	5	Out	12	42	142	63	68	34	34
		In	4	72	...	..	78	42	36
		Out	4	40	...	..	82	42	40
		In	4	70	144	62	80	50	30
	6	Out	12	40	150	57	66	38	28
		In	4	70	...	..	72	43	29
		Out	4	50	...	..	64	30	34
		In	4	70	162	82	62	32	30
	7	Out	12	35	115	50	60	36	24
		In	4	70	110	42	78	50	28
		Out	4	40	...	..	78	52	26†
		In	3	70	115	38	74	46	28
No. 6716 Age, 5 years Right lower lobe, mod. severe	8	In	Ent.	72	140	37	100	58	42
		Out	3	40	...	..	100	62	38
		In	3	72	145	42	100	60	40
	9	Out	12	35	140	32	102	63	39
		In	5	70	...	..	98	54	44
		Out	3	50	...	..	98	55	43
		In	4	72	145	48	100	60	40
	10	Out	12	40	140	35	94	58	36
		In	4	72	...	..	97	59	38
		Out	4	48	...	..	98	60	38
		In	4	70	148	48	100	58	42
	11	Out	12	40	100	24	98	60	38†

PROTOCOLS OF DATA ON THIRTY-TWO CASES OF PNEUMONIA UNDER COLD-AIR TREATMENT

Number, Age, Nature of Disease	Day of Disease	Outdoors or In	Hours	Temperature of Place	Pulse	Respiration	Blood Pressure		
							Systolic	Diastolic	Pulse
No. 000?	4	In	Ent.	70	150	53	78	45	33
Age, 3½ years		Out	4	35	140	48	76	40	36
Left lower lobe, severe		In	4	72	136	37	76	42	34
	5	Out	12	32	140	42	78	48	30
		In	4	70	132	42	74	42	32
		Out	3	35	148	50	74	40	34
		In	3	68	148	43	70	40	30
	6	Out	12	35	140	38	72	38	34
		In	4	70	134	40	68	34	34
		Out	4	32	152	47	70	40	30
		In	4	70	135	32	68	36	32
	7	Out	12	30	160	48	70	40	30
		In	4	70	148	46	70	45	35
		Out	4	35	158	50	72	42	30
		In	4	70	140	43	70	40	30
	8	Out	12	28	150	36	68	36	32
		In	4	72	148	45	62	36	26
		Out	4	35	158	38	70	42	28
		In	4	70	108	40	72	38	34†
	9	Out	12	25	102	36	78	45	33
No. 6583	4	In	Ent.	70	160	80	85	40	45
Age, 8 years		Out	4	50	145	70	82	45	37
Both lower lobes, severe	5	In	12	70	132	60	90	50	40
		Out	4	40	148	70	100	65	35
		In	4	72	148	62	100	62	38
		Out	2	32	135	62	98	59	39
		In	2	70	142	65	96	62	34
	6	Out	12	32	140	62	98	65	33
		In	4	70	145	63	100	65	35
		Out	4	35	142	62	95	60	35
		In	4	70	155	80	92	55	37
	7	Out	12	30	147	75	98	57	41
		In	4	70	120	70	100	58	42
		Out	4	35	110	68	100	60	40
		In	4	72	105	62	95	55	40
	8	Out	12	30	118	68	102	64	38
		In	4	68	120	72	98	62	36
		Out	4	35	118	72	90	50	40
		In	4	70	98	35	88	52	36‡
		Out	12	30	92	40	85	54	31
		In	4	70	88	35	82	52	30

The blood pressure readings were taken 198 times after the child had been out of doors from one to eighteen hours, and 154 times after the child had been in from one to twelve hours. The results of these readings are shown in Tables 1 and 2.

TABLE 1.—BLOOD PRESSURES AFTER BEING OUT OF DOORS

	No.	Per Cent.
Rise in systolic pressure	63	31 +
Fall in systolic pressure	105	53
No change in systolic pressure	30	15 +
Rise in diastolic pressure	86	43 +
Fall in diastolic pressure	88	44 +
No change in diastolic pressure	24	12 +
Rise in pulse pressure	67	34 —
Fall in pulse pressure	101	51
No change in pulse pressure	30	15 +

TABLE 2.—Blood Pressures after Being in Ward

	No.	Per Cent.
Rise in systolic pressure	65	42+
Fall in systolic pressure	62	40+
No change in systolic pressure	27	17+
Rise in diastolic pressure	58	37+
Fall in diastolic pressure	79	51+
No change in diastolic pressure	17	11+
Rise in pulse pressure	80	52—
Fall in pulse pressure	55	36—
No change in pulse pressure	19	12+

It is evident from these tables that the temperature of the surrounding air had no constant effect on the systolic, the diastolic or the pulse pressure. It is further noteworthy that both the systolic and the diastolic pressure rose more often after the children had been in the warm air of the ward for some hours than after they had been out in the cold for a number of hours. Further analysis of the protocols shows that, whether the change was from warm to cold or from cold to warm, the variations in the blood pressure were as a rule slight and within the limits of possible errors in observation. It also shows that the variations in pressure bear no relation to the temperature of the outdoor air or the duration of the stay out of doors.

A study of the protocols in detail shows, moreover, that there was no definite relation between the systolic pressure, the diastolic pressure or the pulse pressure and the severity of the disease. Relatively high pressures and relatively low pressures, systolic, diastolic and pulse, were found in all types of the disease. No constant relations of any sort can be made out. These statements are equally true as regards the fatal cases.

The rates of the pulse and respiration were counted in many instances at the same time that the blood pressure was taken, to determine, if possible, what effect the temperature of the surrounding air had on them. The rate of the pulse was counted 166 times after the child had been out of doors for a number of hours, and 130 times after it had been in the ward for several hours. Tables 3 and 4 show the results of these observations.

TABLE 3.—Pulse Rate after Being Out of Doors

	No.	Per Cent.
Increased	57	34+
Diminished	97	58+
Unchanged	12	7+

TABLE 4.—Pulse Rate after Being in Ward

	No.	Per Cent.
Increased	64	49+
Diminished	52	40
Unchanged	14	10+

These tables show that the temperature of the surrounding air had no constant effect on the rate of the pulse. In general, however, the tendency was for the pulse rate to be lower out of doors than in the ward. In many children, nevertheless, there was no relation whatever between the pulse rate and where the child was, the rate varying sometimes in one way and sometimes in the other. In a few instances the pulse rate was usually higher when the children were out of doors. The pulse rate was usually lower when the patients had been out for twelve hours or more than when they had been out but a few hours. There were, however, many exceptions to this rule. It must also be remembered that these long hours were almost always at night and that the pulse rate was taken in the morning after a long rest and at the time when the pulse rate is normally the lowest.

The rate of the respiration was counted 168 times after the child had been out of doors for a number of hours and 137 times after it had been in the ward for several hours. Tables 5 and 6 show the results of these observations.

TABLE 5.—Rate of Respiration after Being Out of Doors

	No.	Per Cent.
Increased	49	29+
Diminished	94	56
Unchanged	25	14+

TABLE 6.—Rate of Respiration after Being in Ward

	No.	Per Cent.
Increased	71	51+
Diminished	58	42+
Unchanged	8	6—

These tables show that the temperature of the surrounding air had no constant effect on the rate of the respiration. In general, however, there was a decided tendency for the rate of the respiration to be lower out of doors than in the ward. There were, nevertheless, many instances in which there was no evident relation whatever between the temperature of the air and the rate of the respiration. In some instances, indeed, the respiration was always more rapid when the child was out of doors.

The impression of the house officers and nurses, who were constantly with the patients, was that, in general, the children were more comfortable out of doors than in the ward. They thought that they coughed less, were quieter, had a better color, and took their food better out of doors than when they were inside. These were, however, merely their impressions, and are, therefore, of little or no scientific value.

The mortality in this series of cases, 25 per cent., was exceptionally high. It shows nothing as to the effect of the cold-air treatment on

the mortality, however, because these patients were not treated consistently either out of doors or in the house. The statistics at present available are, moreover, entirely insufficient to justify any positive conclusions as to what influence the cold-air treatment of pneumonia in children may have upon the mortality. An analysis of all the cases of pneumonia treated at the Children's Hospital since its foundation, made by Cunningham,[7] shows that the mortality at this hospital has been slightly higher since the introduction of the cold-air treatment than it was before. This fact does not prove at all, however, that the increased mortality was due to the cold-air treatment. It is far more probable that it was caused by the well-recognized increase in the virulence of this disease during recent years.

CONCLUSIONS

The following conclusions seem warranted:

There is no constant relation between the systolic, the diastolic or the pulse pressure and the severity of the pneumonia or the temperature of the surrounding air.

The rates of both the pulse and the respiration show a tendency to vary directly with the temperature of the surrounding air.

The patients symptomatically seem more comfortable when they are out of doors than when they are in the house.

No conclusions are justified as to the effect of the cold-air treatment on the mortality of pneumonia in childhood.

7. Cunningham: Boston Med. and Surg. Jour., 1916, clxxiv, 753.

ACETONE BODY PRODUCTION IN INFANCY AND CHILDHOOD*

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In the course of a number of diseases in infancy and childhood acetone bodies are excreted in the urine in sufficient quantity to be detected by qualitative tests. Acidosis may or may not be present; but in the overwhelming majority of cases with acetonuria acidosis is absent. This statement requires explanation because of the frequent confusion of the two terms, "acetonuria" and "acidosis," which are not synonymous. At one time it was justifiable to consider them so. That was shortly after Stadelmann, Minkowski, Külz and others had shown that the high ammonia coefficient of the urine, which Hallervorden had demonstrated with severe diabetes, was dependent on the presence of beta-oxybutyric acid and its closely associated compound aceto-acetic acid, from which acetone is derived.

As time has gone on, however, it has appeared, first, that a severe disturbance similar to that frequently produced by these acids may be brought about by other substances than beta-oxybutyric and aceto-acetic acids; and, second, that the acetone bodies may appear in the urine, in considerable quantity, in the course of disease or even in starvation, without producing disturbance of any kind. Acidosis has therefore come to mean the disturbance which results from a relative excess of acid radicals in the body, acid radicals of any kind, rather than the detection of one or more of these in the urine by colorimetric tests. The salts of those acids that produce acidosis are not essentially toxic. The acids do harm merely because they are acids and neutralize the bases of the body. Under ordinary circumstances acids that are formed in the body or introduced with the food are neutralized and excreted by the kidneys. But the body has the capacity to neutralize and excrete much more, so that if a moderate amount of acid, such as aceto-acetic or beta-oxybutyric, is formed, it is neutralized and excreted with no important loss of base and there is nothing to indicate an excess of acid formation but an analysis of the urine. There is acetonuria, but no acidosis. If acid is ingested or formed in too great excess or not properly eliminated, the bases of the body are withdrawn

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and the alkali reserve is diminished. There is acidosis, but there is no acetonuria unless the acids in excess are those of the acetone series.

The amount of acid that is ingested and formed and excreted in health is very large; the amount of aceto-acetic acid and its decomposition product, acetone, that is required to give qualitative tests in the urine is insignificantly small, only a fraction of 1 per cent. of the total acid excretion. No impression is made upon the alkali reserve by such an amount. It cannot be denied that under certain circumstances beta-oxybutyric and aceto-acetic acids are produced in quantities sufficient to reduce the alkali reserve; then and only then may acidosis properly be said to be present. This diminution in the alkali reserve is shown clinically by hyperpnea, that is, deep breathing of the air hunger type. In the absence of this, which is not always easy to appreciate in its early stages, laboratory tests of a relatively simple character are required.[1] The diagnosis cannot be made from a qualitative examination of the urine.

The production and excretion of the acetone bodies is not an abnormal process. The amounts present in the urine are usually too small to give colorimetric tests. They may be determined by quantitative methods. Veeder and Johnson[2] have shown the average daily excretion of the ketones (presumably acetone and aceto-acetic acid) to be 32 mg. and that of beta-oxybutyric acid to be 38 mg. The acetone bodies may also be shown to be present in the blood, as we have frequently demonstrated by a method devised by one of us.[3] The amount in health is from 1 to 15 mg. per 100 gm. of blood.

The statement is repeatedly made that the appearance of acetone in the urine indicates a mild metabolic disorder, that aceto-acetic acid is found when the disturbance is greater and that it is only when a serious or dangerous breakdown of the chemical processes occurs that beta-oxybutyric acid is to be found. This is far from the truth. When acetone is present in the urine, and this is the case even in health, aceto-acetic acid is present in considerably larger amount, generally from eight to ten times as much, and beta-oxybutyric acid is present in approximately the same quantity as the aceto-acetic acid. The misconception on this point arises because the nitroprussid test, which is ordinarily used for acetone, is in reality an extraordinarily sensitive test for either acetone or aceto-acetic acid. The ferric chlorid test is a much less delicate one for aceto-acetic acid. The tests for beta-oxybutyric acid are less delicate still. When, therefore, it is said that the nitroprussid test shows acetone and the ferric chlorid test no aceto-

1. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 65.
2. Veeder and Johnson: Am. Jour. Dis. Child., 1916, xi, 291.
3. Marriott: Jour. Biol. Chem., 1914, xviii, 507.

acetic acid, it means that both are present but only in small amount and that beta-oxybutyric acid is present also.

The preponderance of beta-oxybutyric acid obtains likewise in the blood, for Marriott,[4] Sassa,[5] and, recently, Moore[6] have shown that there is in health usually twice as much or more of this substance than of acetone and aceto-acetic acid combined.

Clinically, we know that acetone bodies are to be found very frequently in the urine of sick children, though we usually do not take the trouble to look for them. Thus, Holt[7] reported that in 30 per cent. of 200 consecutive cases admitted to the Babies' Hospital the acetone bodies were found in the urine, and that they were present with 70 per cent. of the cases of pneumonia. Frew[8] found positive tests for the acetone bodies in the urine of more than 60 per cent. of 662 consecutive patients admitted to the Great Ormond Street Hospital. Ludwig Meyer[9] found a positive Legal's test in the urine of 70 per cent. of patients with diphtheria, of 69 per cent. of those with scarlet fever and of 60 per cent. of those with measles. Acetonuria is certainly common enough with febrile disease, but it is found in many other conditions as well, such as after anesthesia and particularly with partial or complete starvation. Indeed, partial inanition is probably the chief cause. This partial inanition, the result of anorexia in fever or the result of the increased metabolism during the fever, almost inevitably produces acetonuria. If, then, we rely on qualitative urinary tests, such as the nitroprussid and the ferric chlorid, and when they are positive, make diagnosis of acidosis, we can at almost any time and in any place detect an epidemic of acidosis. We reduce the art of diagnosis to the lowest terms and acidosis becomes the most frequent of children's diseases. Acidosis is a frequent condition in infancy and childhood and it is a very important one and very serious, but it is usually not due to the production of the acetone bodies. It is frequent and very fatal with severe diarrhea, as we have shown; it occurs with severe nephritis and with burns, but in such conditions it is not dependent on the acetone bodies. And even when the acetone bodies are to be detected in great quantity, it is necessary, in order to demonstrate that their presence is injurious, to observe hyperpnea or to prove a diminution of the alkali reserve on which the hyperpnea depends. If this is done, here and there a case of acidosis may be detected, but it can confidently be asserted that these cases will not be found in numbers sufficient to announce the occurrence of an epidemic.

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4. Marriott: Jour. Biol. Chem., 1913, xvi, 293.
5. Sassa: Biochem. Ztschr., 1914, lix, 362.
6. Moore: Am. Jour. Dis. Child., 1916, xii. Now in press.
7. Holt: Jour. Am. Med. Assn., 1916, lxvi, 144.
8. Frew: Lancet, London, 1911, ii, 1264.
9. Meyer: Jahrb. f. Kinderh., 1905, lxi, 438.

The cases that we have studied have been considered rather from the viewpoint of the acetone bodies found in the blood than from the amount eliminated in the urine, since this gives more information in regard to the conditions obtaining at a certain definite time. We have studied the cases also for evidences of acidosis by a number of methods that determine the carbon dioxid tension of the alveolar air and the alkali reserve.

Formerly, diabetes in childhood was accompanied by an enormous increase in acetone body excretion. Death usually took place in coma. With the method of treatment introduced by Allen it is possible to prevent the production of the acetone bodies to such an extent that they may remain, for a long time at least, within normal limits. This we have been able to do with four recent patients, one of whom has been under observation for four years and another for two. The acetonemia of diabetes treated by carbohydrate reduction is frequently not greater than that which we have observed after simple starvation in normal children.

In several cases of ileocolitis there has been found a very marked acetonemia; in one instance the acetone bodies in the blood increased in a day from 16 to 183 mg. per 100 gm. of blood. Another of these children, only 2 years of age, passed more than 8 gm. of these bodies in the urine in twenty-four hours. Acidosis, that is, a diminution in the alkali reserve of the body, was demonstrated in three of the cases. The cause of this excessive production of the acetone bodies is not clear. It far exceeds anything that would result from starvation alone and occurs much more rapidly. These cases are in striking contrast with those of diarrhea of the choleriform type; for in these latter, even when most extreme acidosis is present, the acetonemia is slight. It is often less than in cases of diarrhea without acidosis, and entirely insufficient to be a factor in the disturbance of the acid base equilibrium.

It has long been recognized that acetonuria frequently accompanies vomiting in childhood. Perhaps it is to Marfan[10] that the chief credit is due for emphasizing the regular presence of the acetone bodies in the recurrent, periodic or cyclic type of vomiting. The acetone bodies are so frequently present in recurrent vomiting and often appear so early that tests for their presence are utilized by many in the differential diagnosis of the condition. They have been found even before the vomiting and can often be detected in the urine by qualitative tests at the time of the first vomiting. The chief interest attaches to the mechanism of production of these substances. The most frequent cause of acetonuria is partial or complete starvation. Certainly in many of these cases acetonuria cannot result from starvation, for the

10. Marfan: Arch. de méd. d. enfants, 1901, ix, 641.

period of abstinence from food is altogether too short. Nor can the acetonuria be considered comparable to that which occurs in diabetes, for sugar is never found in the urine. Hilliger[11] was able to produce attacks of vomiting with acetonuria in one child merely by limiting the ingestion of carbohydrates. When the blood sugar fell to a point somewhat below the normal, that is, 0.07 per cent., vomiting took place. It would seem that the metabolism of the patient whom he studied must have been singularly unusual. Children as a rule will not suffer such a rapid diminution of blood sugar as did his patient, nor will vomiting occur with those subject to recurrent vomiting from the reduction of carbohydrate in the diet for only a few hours. We have found no constant relationship between the sugar content of the blood and the onset of attacks.

More data in regard to the glucose content of the blood in this condition, between and during attacks, are desirable. We are left without an explanation of why there is this rapid and excessive production of the acetone bodies in perhaps the majority of the attacks. It must be recognized that they cannot be held responsible for the vomiting, but rather that they accompany it and that both are better to be considered as evidences of a deep-seated metabolic disturbance, or, as Marfan suggests, of an intoxication analogous to that resulting from the administration of ether or chloroform. It is a metabolic disturbance that leaves no trace, for we cannot consider the insignificant postmortem findings that have been reported in the few fatal cases such as slight hemorrhagic erosions and fatty liver, as satisfactory explanations of death.

Despite the undoubted frequency of this condition, death is very unusual. The great majority of the children do not have acidosis, that is, there is no diminution in their alkali reserve and they recover without alkali therapy. Some may, however, develop acidosis and a very few die apparently from the acidosis. A case of mild acidosis with recurrent vomiting was the following:

A girl of 3½ years began with vomiting, which lasted four days. On the third day there was slight hyperpnea, an appreciable diminution of the alkali reserve,[12] and the acetone bodies in her blood were 84.5 mg. per 100 gm. of blood. By giving sodium bicarbonate her alkali reserve was renewed, and shortly after the cessation of the vomiting she was as well as usual. She has since had other attacks.

A fatal case that we have already reported was briefly as follows:[1]

A colored boy 3½ years old began to vomit without apparent cause when on a rational diet. The vomiting was continuous, nothing being retained. His condition rapidly became worse and he was brought to the hospital at the end of forty-eight hours in coma and with hyperpnea. There was a great reduction

11. Hillinger: Jahrb. f. Kinderh., 1914, lxxx, 1.
12. RpH of the serum, 8.2. See Marriott: Arch. Int. Med., 1916, xvii, 840.

in his alkali reserve and his blood contained the surprising amount of 170 mg. per 100 gm. of blood. This approximates the amount found in diabetic patients with coma. The acetone bodies were quite plainly the cause of the acidosis. He died shortly after admission. The necropsy revealed no satisfactory explanation for death.

This was the boy's first attack of excessive vomiting, but the continuous and severe vomiting without any determinable cause in life or post mortem makes it apparent that it should be included among the cases of vomiting with acetonuria. There are other cases that are not so clear, in which the vomiting is slight or entirely absent and in which the acetonemia dominates the whole picture. Two cases that we have observed were as follows:

(1) A boy of 3 years, with a renal tumor and a metastasis in the antrum of Highmore, vomited two or three times one day, but not thereafter. He complained of a sensation of breathlessness. This gradually increased and thirty-six hours later he was in much distress with marked hyperpnea. There was no cyanosis. All the tests showed acidosis, that is, a distinct diminution in his alkali reserve.[13] He was given sodium bicarbonate by mouth, by rectum and intravenously. This last method of administration brought about almost instantaneous relief and in forty-eight hours he was quite as he was before the attack. He passed 16 gm. of beta-oxybutyric acid and 4 gm. of aceto-acetic acid in his urine in twenty-four hours. Four weeks later, a similar attack, nearly as severe, occurred without any vomiting. This was also promptly terminated by an intravenous infusion of sodium bicarbonate.

(2) A strong, vigorous infant of 1 year of age, who had been exclusively breast fed, began suddenly with vomiting, which was not long continued. He was irritable and restless and later became drowsy. Three days after the onset hyperpnea was noticed, and four days after this it was intense. He was in stupor with a fever of 101.5 F. All the laboratory tests were conclusive of acidosis.[14] His blood contained 136 mg. of the acetone bodies per 100 gm. He died less than twenty-four hours after admission to the hospital.

The cause of the acetonemia in such cases is as obscure as it is with recurrent vomiting. It certainly does not result from deficiency of carbohydrates in the food. It is perhaps best to look on all of these cases, including those of recurrent vomiting with early and severe acetonemia, as really one condition. The vomiting may, in some cases, be present and continuous, in others it may be slight or entirely absent. The vomiting thus would not be considered an essential feature. Theorizing is permissible, but does not yield much information unless supported by direct observations concerning the chemical processes of intermediary metabolism. It is of importance from the therapeutic point of view to recognize that acetone body acidosis sufficient to cause death may arise spontaneously and without vomiting. Overcoming the acidosis when it is very severe is the essential factor in treatment, for the acetonemia arises rapidly and apparently spontaneously, but the

13. Sellards' test colorless on evaporation; pH of serum, 7.2.

14. Tension alveolar carbon dioxid 20 mm., pH of serum, 7.2, RpH of serum, 7.75.

excessive production of acids ceases also spontaneously and rapidly. It is self-limited and does not depend on chronic disease, even though the attacks may be repeated.

SUMMARY

Acidosis and acetonuria are not synonymous terms.

There is no justification for believing that acidosis due to the acetone bodies occurs in epidemic form.

Deficient food or increased requirement for food (disproportion between caloric intake and output) is the chief cause of acetonuria, but this rarely results in acidosis.

The production of acetone bodies occurs at times when starvation cannot be held responsible. The production is rapid and excessive and sufficient to cause a severe or fatal acidosis. This condition is not necessarily accompanied by vomiting. It probably depends on the same underlying metabolic disturbance as do the majority of cases of recurrent vomiting.

PROVOCATIVE AND PROPHYLACTIC VACCINATION IN THE VAGINITIS OF INFANTS*

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We have had to contend with the problem of vaginitis, just as so many others have had to do in similar institutions. It is not my intention to write a review of the trials and tribulations encountered during the five years since we have been housed in modern buildings and have made every effort to combat this insidious disease. As we have profited in some respects by experience, however, it seemed as if it might be of value to those who are actively interested in this problem to communicate briefly some of the lessons learned during this period.

Our endeavors have been directed in various directions: in preventing the admission of infected infants, in attempting in many different ways to avoid a spread of infection, in diagnosing cases at the earliest possible moment, and, finally, in resorting to every means to effect a cure. It should be realized at the outset, although the distinction is not always sharply drawn, that vaginitis presents a problem in a home or asylum for infants totally different from that which it presents in a hospital. In the latter the solution is comparatively simple, for all that is necessary in order to eradicate the disease is to cease admitting girl infants and to discharge those infected, one by one, as they are cured of the ailment for which they were admitted to the hospital. In the asylum, on the other hand, when a case of vaginitis slips past the admitting physician, or arises apparently de novo in one of its wards, it is realized that a heavy burden has fallen on the medical staff, for this infant will have to be guarded under quarantine for months or years, and will at all times constitute a threatening source of infection. We have had a variable degree of vaginitis; at times a lull, at others a sudden increase in numbers. At present, due to the regulations which are in force, the number of cases is comparatively few. It may be remarked, however, that during these years no instance of ophthalmia, of arthritis, or of infection of any of the personnel has occurred. There have been four instances of specific urethritis in boy infants, and one of rectal infection. This urethritis lasted but a few weeks and

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* From the Research Laboratory, Department of Health, New York City, and the Home for Hebrew Infants.
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did not give rise to a positive complement fixation reaction, so that we believe it involved merely the anterior urethra.

The diagnosis of gonococcus vaginitis is not always easy to establish. In the first place, it is at times confused with other types of this disease, for there is no doubt that this inflammation may be due to micro-organisms other than the gonococcus. For months we harbored a case due to the streptococcus, which was present in almost pure culture in the vaginal discharge, and was furthermore identified on postmortem examination from cultures taken from the cervical canal. There was an absence of gonococci both during life and after death. These, however, are not the difficult instances we refer to, but the borderline cases, which are exceedingly puzzling, especially those showing merely pus cells on microscopic examination. If these cells are numerous, an inflammation is undoubtedly present, and in the great majority of cases the infecting organism will prove to be gonococcus. The specific nature of this infection is all the more probable if there are no micro-organisms to be seen in the field among the cells. One exception should be borne in mind as to the diagnostic significance of pus cells. This subject was called to our attention by noting many leukocytes in the smear of an infant only 48 hours old, who was brought to the institution for admission. It hardly seemed as if this were an instance of gonococcus vaginitis, although it is perfectly possible for an infant to be infected in this way during parturition, so we had some tests carried out in order to ascertain how often pus cells are encountered in smears taken from infants during the first two days of life. These tests were kindly carried out by Dr. Edwin Langrock. They showed that in about 50 per cent. of infants pus cells may be found in vaginal smears taken within the first forty-eight hours of life, so that it would seem that they must not be regarded as pathologic, but probably as the reaction of the external tissues to the inevitable invasion by bacteria. Possibly a similar inflammatory reaction occurs in the intestinal canal.[1] It should be understood that for these vaginal smears, as well as all others referred to in this paper, an applicator tipped with moistened cotton was inserted deep into the vagina, so as to come in contact with the cervix.

As we inquire deeper into the cause of the spread of vaginitis, it would seem to resolve itself, in the last analysis, to a consideration of but one more phase of the general problem of the dangerous but healthy carrier. Although there can be no doubt that the disease is frequently communicated by means of clothing or utensils, the fundamental cause of the infection of one or more infants, in institutions where every

1. In this connection it would seem of interest to note that leukocyte counts of new-born infants were found frequently to be high, the total per cubic centimeter reaching from 15,000 to 23,000, with a differential cell count presenting the adult type, namely, from 60 to 75 per cent. of polymorphonuclears.

care is exercised, must be considered the latent carrier, some healthy infant who harbors the gonococcus. Such has been our experience. For two years a pathologist devoted about two hours daily to the making of routine microscopic examinations of vaginal smears of the infants in the asylum. Wherever a case of vaginitis arose, the routine procedure was to make examinations three times during the following week on every infant in the ward in order to ferret out the source of the infection. A card catalogue was kept both of the individual infants and the various wards. Repeated tests brought to light some case in which, in spite of the absence of discharge, gonococci were evident in the smears. Recrudescences of infection occurred in one ward or another every few months and sometimes oftener. We are confronted, therefore, with a problem similar to that in typhoid or diphtheria, in which the carrier constitutes the main stumbling block in the path of prophylaxis. In the case of vaginitis the solution is rendered still more difficult in view of the heightened susceptibility of infants to infection.

During the past five years necropsies have been performed on four infants who had vaginitis while in the institution. (We are able to carry out postmortem examinations on fully 75 per cent. of the children who die.) This offered an exceptional opportunity to gain an insight into the pathologic changes of the common nonvirulent form of this infection. The pathology of this disease is generally glossed over in textbook descriptions. Furthermore, judging from the literature, we conclude the number of postmortem examinations of cases of this type is not large. We should expect this to be the case, as very few hospitals admit vaginitis, which must therefore constitute merely a chance pathologic condition met with in the course of some primary fatal disease. One of our cases had existed but three weeks, two patients were known to have had vaginitis for months, and one for a year or more. They all showed the same pathologic condition, which may be summarized in a few lines: Macroscopically the vagina appeared negative, as did the body of the uterus and the appendages. The only abnormal condition was redness of the tip of the cervix, which, however, did not extend along the canal to the internal os. Microscopic examination confirmed the gross anatomic appearance of these structures. In every instance the entire vagina, the uterus and the tubes were removed for microscopic examination, which was kindly carried out by Drs. Eli Moschowitz and Alwin Pappenheimer, whom I take pleasure in thanking for their courtesy in this connection. The sole lesion was an inflammation of the cervix about the external os, a round-cell infiltration of the submucous tissues. Guided by these postmortem examinations, we must regard, it would seem, the average gonococcus infection as involving the cervix rather than the vagina, and must consider the infection a cervicitis rather than a vaginitis. It

is in the cervix that the gonococcus finds a most favorable nidus. In a study published a few years ago from this service by Rubin and Leopold,[2] an inflammation of the cervix was frequently seen by direct examination. In the recent preliminary report of the vaginitis committee of the American Pediatric Society[3] it may be noted that eleven gynecologists who responded to their questionnaire thought that the cervix or uterus at times showed evidences of this disease. In the adults it has been reported that 95 per cent. of the chronic cases showed a cervicitis.[4] As the result of personal experience we must conclude that the vagina is comparatively immune in this infection, especially when the disease has reached the subacute or chronic stage.

There seems to exist a very general impression that vaginitis is more particularly a disease associated with child-caring institutions, and that infants brought up in the homes of the poor are infected far less frequently. This has not been our experience. During the year 1915 sixty-six infant girls were admitted to the institution and seventy-two rejected; of these seventy-two, sixty were refused admission on account of vaginitis, thus making the total infection noted in these children almost 50 per cent. It should be added that only three of the rejected patients were referred from other institutions, and that the remainder came direct from their homes. Further investigation may possibly show that this ratio of positive cases is exceptionally high. As a result of having to refuse so many infant girls the institution now harbors one-third girls and two-thirds boys. It would be of theoretical as well as of great practical interest if we could know the results of a similar examination of older girls. From a limited experience of girls between the ages of 4 and 10 at the Tuberculosis Preventorium, I may state that not a few children of this age show signs of infection, although the danger of the spread of the disease seems to have become greatly lessened at this age.

One of the great difficulties in trying to combat vaginitis or cervicitis is that we find it impossible to recognize the infectious case in its earliest stage, in other words, the danger of the latent carrier. To overcome this difficulty we have made many attempts to convert the carrier into an open or florid case. Various drugs have been injected into the vagina in order to bring this about, but as they were found of no practical value, it would serve no purpose to enter into detail concerning efforts of this kind. For the past year, with this end in view, all infant girls have received three subcutaneous injections of gonococcus vaccine soon after they were admitted to the institution. These infants, it should be understood, had all shown an absence of pus cells on admission. The vaccine was prepared from a culture isolated

2. Rubin, I. C., and Leopold, J. S.: Am. Jour. Dis. Child., 1913, v, 58.
3. Tr. Am. Ped. Soc., 1915, xxvii, 331.
4. Menge, K.: Handbuch der Geschlechtskunde, Vienna, 1912, ii, 323.

from one of the cases in the institution, and 250, 500, and 750 millions were injected with three day intervals. The object of these vaccinations was to determine whether they would prove provocative and bring to light latent infections. In adults with urethritis it has been found by Asch[5] that injections of vaccine lead to a discharge containing pus cells and gonococci. The dosage which we used was entirely empirical. As a result of experience it would seem that it could be much smaller; indeed, at the present time we are giving only 100, 200 and 400 millions. Moreover, two injections may prove sufficient, as we have rarely brought about a discharge by means of a third inoculation. During the past year such provocative injections have led to the discovery of eight new cases during the first week or two following their admission (Table 1), and to the unprecedented result that not one case of vaginitis has slipped into the main institution from the admitting pavilion. We have made use of this diagnostic aid not only at the time of admission, but in order to discover carriers in dormitories, where sometimes sporadic cases of vaginitis arose (Table 2). For example, in one ward of twelve infants in which the girls had been free from vaginitis for a period of six to eighteen months, an active case suddenly developed, and although cervical smears failed to disclose its source, two carriers were brought to light by means of provocative inoculations. This has been the case on other occasions. This spring one case of vaginitis with gonococci and another showing pus cells, but no micro-organisms, was unexpectedly and unaccountably noted in the infirmary. There were six infant girls at the time in this ward. Provocative inoculation disclosed four positive cases after a second inoculation. Here was a veritable latent epidemic, which was uncloaked by means of the vaccine.

We are unable to state the exact scientific basis of the reaction following these inoculations. It is, however, not due to a rise of temperature. This was evident, as it occurred to a marked extent in some instances in which there was no febrile reaction whatsoever. It cannot be regarded as absolutely specific, for a positive result was brought about at times by similar injections of staphylococcus vaccine, although this was not found to be so reliable for this purpose as that made from the gonococcus. Indeed it is becoming more and more evident that many similar reactions of the tissues which we have been wont to regard as specific in nature, must be considered in large measure systemic cellular reactions. Whatever may prove to be its exact scientific basis, we firmly believe that it will be found of great practical aid in combating this difficult infection. The same principle might perhaps be applied to facilitate the recognition of carriers in other infections, for example, typhoid fever and pyelitis.

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5. Asch, P.: München. med Wchnschr., 1915, No. 39.

TABLE 1.—ROUTINE PROVOCATIVE VACCINATIONS

Name	Age	Admitted	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
M. G.	8 mo.	11/15/14	.....	11/15/14	—	—	—	—	Date of vaccination is always that of the first injection; two other injections were given at three day intervals
				12/12/14	—	+	+	—	
			4/27/15	4/25/15	+	+	+	—	
				5/ 1/15	+	+	+++	+	
				5/ 3/15	+	+	+++	+	
A. S.	11 mo.	4/15/15	.....	4/15/15	—	—	—	—	Smear after third injection loaded with gonococci; discovered in reception pavilion
				4/20/15	—	—	—	—	
			4/24/15	5/ 6/15	+	+	+	+	
				6/ 1/15	+	+	+	+	
				7/10/15	+	+	+	+	
				9/ 8/15	—	+	++	+	
H. B.	8 mo.	12/21/15	.....	12/21/15	—	—	—	—	Vaccine given a second time to discover latent infection in this ward
			2/ 2/16	2/ 9/16	—	—	—	—	
				2/25/16	—	—	++	—	
			3/ 1/16	3/16/16	—	+	++	—	
				3/29/16	—	+	++	+	
R. G.	11 mo.	12/14/14	.....	12/14/14	—	—	—	—	Vaccinated in order to find gonococci; a discharge resulted which lasted about a month and a half
				1/ 9/15	—	+	—	—	
				3/ 1/15	—	+	++	—	
			4/27/15	5/ 5/15	+	+	+	+	
				6/ 1/15	+	+	+	+	
E. S.	3 yr.	11/ 1/15	.....	11/ 1/15	—	—	—	—	Vaginal discharge incited, which lasted about three weeks
			11/21/15	11/29/15	+	+	+	+	
				12/16/15	+	+	+	+	
				3/ 7/16	—	—	—	—	
				3/10/16	—	+	+	+	
				4/11/16	—	+	+	—	
M. H.	3 yr.	7/13/15	.....	7/13/15	—	—	—	—	Vaginal discharge incited, which lasted about two weeks; discovered in reception pavilion
			7/15/15	7/29/15	+	+	+	+	
				8/ 3/15	—	±	+	+	
				8/ 9/15	—	—	—	—	
				3/10/16	—	+	+	—	
				4/14/16	—	—	+		

TABLE 2.—Provocative Vaccination in Old Cases of Vaginitis, Latent Carriers

Name	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
S. L.	.....	1/15/14	+	+	+	—	Positive result after negative period of two years
		12/20/15	—	—	—	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 6/16	—	—	+++	—	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	+	—	
F. G.	.....	11/ 8/14	—	+	—	—	No temperature reaction
		12/20/14	—	+	+	—	
		12/20/15	—	—	+	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 6/16	—	—	+	—	
		2/ 9/16	—	—	+	—	
		4/20/16	—	—	+++	++	
		5/ 7/16	—	—	+	—	
L. E.	.....	11/ 8/14	—	+	+	—	No temperature reaction
		12/20/14	—	+	++	—	
		12/20/15	—	—	+	—	
		12/30/15	—	—	+	—	
	2/ 1/16	2/ 6/16	—	—	++	—	
		2/ 9/16	—	—	+++	+	
		4/20/16	—	—	—	—	
G. S.	.....	11/10/14	—	+	+	+	
		12/ 8/14	—	+	++	—	
		1/20/15	—	+	+	—	
		12/15/15	—	—	—	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 6/16	—	—	+++	+	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	—	—	
F. G.	.....	6/ 8/14	+	+	+	+	
		12/15/14	—	+	+	—	
		1/12/15	+	+	+	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	++	—	
	2/ 1/16	2/ 6/16	—	—	++	—	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	+	+	

TABLE 2.—PROVOCATIVE VACCINATION IN OLD CASES OF VAGINITIS, LATENT CARRIERS—(*Continued*)

Name	Date of Vaccination	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Remarks
R. L.	.....	5/18/14	—	+	++	—	Went home in April
		12/20/14	—	+	+	—	
		12/18/15	—	—	—	—	
		12/30/15	—	—	—	—	
	2/ 1/16	2/ 8/16	—	—	++	—	
		2/ 9/16	—	—	++	+	
S. R.	.....	10/12/14	—	+	—	—	
		12/15/14	—	+	+++	—	
		1/18/15	+	+	+	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	+	—	
	2/ 1/16	2/ 6/16	—	—	++	—	
		2/ 9/16	—	—	++	+	
		4/20/16	—	—	++	+	
B. K.	.....	12/10/14	—	+	—	—	
		1/12/15	—	+	—	—	
		12/20/15	—	—	—	—	
		12/30/15	—	—	+	—	
	2/ 1/16	2/ 6/16	—	—	+	—	
		2/ 7/16	—	—	++	+	
		4/30/16	—	—	+	—	

The vaccine was found to be of value not only as a diagnostic, but, to a certain extent, as a prophylactic measure. To this end we used it on about seventy-five infants and were able to change the entire nature of vaginitis in our institution. In patients who were vaccinated the vaginitis showed a mild type of infection. It is not to be expected that prophylactic injections can prevent the occurrence of carriers, just as diphtheria antitoxin cannot obviate the occurrence of diphtheria carriers, and typhoid vaccine cannot prevent the implantation of typhoid bacilli in the mucous membrane. However, the protected patients, instead of developing a vaginal discharge full of pus cells and gonococci, were found to have no discharge whatsoever, and to show as the only evidence of infection a few pus cells and microorganisms in the cervical smears. In other words, a nonclinical type of disease resulted. The bacteria frequently appear atypical under these conditions; they are degenerated and often very small, as has been described by many in connection with chronic cases. It is too early to state how long this partial immunity will last. We have not

attempted to control its course by means of complement fixation, as our experience with this reaction has not been entirely satisfactory. For three years we made serum tests of this kind on the infants in the institution, in order to judge of the persistence of infection, but the results proved so contradictory that the attempt to solve the question by this means was abandoned.

There are some diseases which occasion not only a recrudescence of vaginitis, but seem to confer a susceptibility to infection. This is especially true of scarlet fever. In this disease the susceptibility extends still farther, in that a systemic lack of resistance to the gonococcus results, so that joint infections and other evidences of a specific bacterial invasion result. Recently Nicoll[6] reported three cases of gonococcus arthritis in children from the scarlet fever pavilion of the Willard Parker Hospital, and others have been noted in these wards from time to time. However, there is not merely an acquired susceptibility and probably also a natural susceptibility to gonococcus infection, but also a well defined natural immunity. This has been very evident in individual instances among the infants in the asylum.

At times it has been very difficult to carry out an absolute isolation of vaginitis patients, more especially when some infectious disease has visited the institution. For example, about two years ago, during a considerable epidemic of whooping cough, it became necessary to isolate the children according to the presence of pertussis rather than according to vaginitis. Under such conditions it was observed that some infants did not develop vaginitis in spite of some months of exposure in these wards. In other words, these babies possessed a high degree of immunity (Table 3). Since then this idiosyncracy has been confirmed by further observations and there are at present five, or possibly six, infants in the institution who may be said to be immune, or almost immune, to this infection, and who during the past two years several times have chanced to be in wards in which vaginitis broke out and who nevertheless each time have escaped infection. These cases have been given provocative vaccination in order to make certain of their freedom from infection, but in every instance this has failed to incite any inflammatory reaction. We do not know whether this is to be considered a local or systemic immunity. We may, however, call attention to the fact that there seems to be no doubt that a similar immunity exists in the adult. It is to be remembered in this connection that there is frequently a difference in the configuration of the epithelium in different individuals. In some, the columnar epithelium begins outside of the cervix, in others the squamous epithelium, which is typical of the vagina, extends even into the cervical canal. These variations, as well as others relating to the number, the size, and the patency of the

6. Nicoll, M.: Arch. Pediat., 1914, No. 11, 804.

TABLE 3.—CASES OF NATURAL IMMUNITY *

Name	Admitted	Age on Admission	Cervical Smear	Vaginal Discharge	Macroscopic Pus	Microscopic Pus	Gonococci	Provocative Vaccination
P. K.	5/29/12	6 mo.	6/24/14	—	+	—	—	
			8/16/14	—	—	—	—	
			9/15/14	—	+	—	—	
			12/30/14	—	+	—	—	
			7/ 8/15	—	—	—	—	
			7/15/15	—	—	—	—	7/15/15
			7/20/15	—	—	—	—	
			3/ 7/16	—	—	—	—	
			5/ 4/16	—	—	—	—	
R. C.	5/23/13	2 yr.	5/24/14	—	+	—	—	
			5/26/14	—	—	—	—	
			6/24/14	—	+	+	—	
			1/ 5/15	—	—	—	—	
			5/14/15	—	+	—	—	
			7/ 9/15	—	+	+	—	7/15/15
			7/20/15	—	+	+	—	
			9/15/15	—	—	+	—	
			12/30/15	—	—	—	—	
			2/24/16	—	+	—	—	
			3/ 6/16	—	—	—	—	
N. S.	4/21/14	3 yr.	7/25/14	—	—	—	—	
			7/ 8/15	—	—	—	—	
			7/10/15	—	—	—	—	
			7/20/15	—	—	—	—	7/15/15
			9/ 7/15	—	—	+	—	
			12/30/15	—	+	—	—	
			2/ 6/16	—	+	++	—	
			3/ 4/16	—	—	+	—	
			5/ 4/16	—	—	+	—	
F. B.	6/16/12	2 yr.	6/24/14	—	+	—	—	
			7/10/15	—	—	—	—	7/15/15
			7/20/15	—	—	—	—	
			9/ 7/15	—	—	+	—	
			12/30/15	—	+	+	—	
			3/ 4/16	—	—	—	—	

* Unavoidably exposed for some months during spring of 1914, due to pertussis epidemic.

cervical glands, have been shown to be present in earliest infancy.[7] As is well known, the gonococcus has a particular affinity for surfaces covered with columnar epithelium, and is not able to attack those lined with squamous cells. This immunity is rare. In many instances it is probably not absolute and sooner or later, in the course of months, it will be found that infection takes place. It is reported as an observation of interest, rather than as one which can play a rôle in the epidemiology of this disease.

CONCLUSIONS

Postmortem examinations show that in the subacute and chronic cases of vaginitis in infants the cervix is most frequently involved and that the vagina generally shows no signs of inflammation. Cervicitis would therefore seem to be a more correct term, in this connection, than vaginitis.

Where numerous pus cells without bacteria are found in smears made from the cervix, an inflammation may be assumed to be present, and in the overwhelming majority of instances the inciting factor will be found to be the gonococcus. Other micro-organisms may, however, be the cause of the inflammatory process, for example a streptococcus, as in a case which was studied both during life and after death. It should be borne in mind that smears taken from new-born infants very frequently show pus cells, probably due to the invasion of the vagina by saprophytic bacteria, and that, in the new-born, they should not be considered pathologic or as evidence of gonococcal inflammation.

Gonorrheal vaginitis, or cervicitis, should not be regarded as a disease encountered especially in institutions, as it may be found in a considerable proportion of infants living in the crowded tenements in the city.

In child-caring institutions the greatest obstacle to limiting and controlling the spread of this disease is the difficulty of recognizing latent cases. It affords, therefore, but one more aspect of the problem of the healthy but dangerous carrier, and of the difficulty of devising methods to prevent contact infection. By means of provocative inoculations of gonococcus vaccine we have found it possible to convert the concealed carrier into an open case, and in this way to discover many cases which had eluded detection. Vaccinations have also some prophylactic value, and may either confer protection or render subsequent infection of a mild character, so that it assumes a bacteriologic rather than a clinical type.

There is not only a natural susceptibility to this infection and an acquired susceptibility, as occurs in the course of scarlet fever, but a natural immunity, which may be sufficient to protect infants who come in contact with infected patients.

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7. Moericke, R.: Ztschr. f. Geburtsh. u. Gynäk., 1882, vii, 84.

PROGRESS IN PEDIATRICS

REVIEW OF THE LITERATURE OF THE PAST TWO YEARS ON THE ORGANS OF INTERNAL SECRETION

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The review which follows is intended to cover those parts of the literature on internal secretions of the past two years which have seemed to the writer to be especially important or interesting. It was found impossible to master the entire literature that has sprung up about this fruitful subject, much less to include it in its entirety in a review, so that some important work may receive no mention. Certain organs known to have an internal secretion, the genital glands and pancreas, and others thought by some to possess an internal secretory function, such as the kidney, have been purposely omitted from consideration for lack of time and space for adequate treatment. On the other hand, the pineal and carotid glands, which have been much exploited recently, have been discussed in some detail, although no certainty exists that they are organs of internal secretion. Pende's "new organ of internal secretion" has been included.

The citations of the literature are not absolutely complete. Certain references which seemed to be of little value have been purposely omitted from the list, and doubtless some important references have been accidently passed over.

THE SUPRARENALS

Thomas,[1] and Elliott and Armour,[2] both writing in 1911, described the histologic changes which occur in the cortex of the suprarenal shortly after birth. It is well known that the suprarenal of the newborn child is considerably larger, relatively speaking, than the suprarenal at a later period of childhood or in adult life. At the third postnatal month it actually weighs less than at birth (Elliott and Armour), although the body weight has increased by one half or two thirds. According to Elliott and Armour the cortex of the suprarenal at birth is composed of a narrow outer rim of cells, from which develops

1. Thomas, E.: Beitr. z. path. Anat. u. z. allg. Path., L, 283; cited by Pappenheimer.
2. Elliott, T. R., and Armour, R. G.: Jour. Path. and Bacteriol., 15, 1911.

the adult cortex, and between this rim and the medulla an enormous mass of fetal cortex, destined almost immediately to disappear. The medulla at birth is a thin core, not much more than a line in thickness, which increases in size progressively as age advances. The largest part of the chromaffin tissue of the new-born child lies outside the suprarenals in the paraganglia of the sympathetic. But these paraganglia dwindle as the medulla of the suprarenal increases. "Generalizing roughly, one may say that the fetal cortex, which was so large, and the fetal paraganglia perish and are replaced by a new cortex and a new medulla, which constitutes the adult gland" (Elliott and Armour). The fetal portion of the cortex of the suprarenal contains at birth blood vessels, but not the lipoid substance, which seems to be the characteristic product of the permanent cortex. Immediately after birth it undergoes fatty degeneration and vanishes, but the outer rim, which contains the characteristic lipoid even before birth, increases in size and forms the permanent cortex of the gland.

Lewis and Pappenheimer[3] have studied the suprarenal gland in a large series of children dying within the first three weeks of life. According to them the degenerative changes appear in the cortex very soon after birth, and are practically complete by the end of the second week. They cause an abrupt diminution in the breadth of the cortex. No regenerative process can be detected during the first three weeks of life. They think the fibrous tissue which in the mature gland separates the medulla from the cortex is formed simply by the collapse of the connective tissue framework of the fetal portion of the cortex as the result of the degeneration and disappearance of its parenchymatous cells. Neither prematurity nor inanition modify the course of the involution.

Kern, who has looked for these changes in the suprarenals of pigs, rabbits, calves, sheep, rats and horses, has been unable to find them. If his observations are correct, the process seems to be peculiar to human beings. Elliott and Armour also state that the suprarenals of animals (they have not examined the suprarenals of the monkey) are smallest at birth and increase in size progressively as age advances, a fact which speaks against the occurence in the suprarenals of animals of the cortical changes in man.

The active principle of the suprarenal (epinephrin) McCord demonstrated in very young beef fetuses by means of the uterus strip method.

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3. Lewis, R. W., and Pappenheimer, A. M.: A Study of the Involutional Changes Which Occur in the Adrenal Cortex During Infancy, Jour. Med. Research, 1916, xxxiv, 81.

J. H. Lewis[4] on the other hand, failed to detect epinephin in the suprarenals of human fetuses, even at term; and Elliott could discover only a trace of the epinephrin in the suprarenals of new-born children, although he found definite evidence of epinephrin in the paraganglion aorticum, a mass of chromaffin tissue situated close to the suprarenals. The epinephrin content of this ganglion was 1/500 of its weight. Similar negative results in human beings have been reported by Moore and Purinton,[5] 1900, and Svehla,[6] 1900, using the older, less accurate chemical methods. The method which Lewis employed for the detection of epinephrin was the chemical method advocated by Folin, Cannon and Denis.[7]

Cannata[8] could find no epinephrin in the blood of new-born children—an experimental result to be anticipated.

Fulk and Macleod[9] report that acid extracts of retroperitoneal chromaffin tissue of man, the dog, cat, rabbit, guinea-pig, white rat, calf, sheep and pig have the same physiologic action on excised strips of intestine and uterus as the active principle of the medulla of the suprarenal gland.

Stewart, Rogoff and Gibson[10] have been able to detect epinephrin in the blood after stimulation of the peripheral end of the splanchnic nerve, according to the method of Joseph and Meltzer. These last-named investigators found that when one cervical ganglion was removed in the rabbit and several days later the peripheral end of the splanchnic nerve stimulated, there occured an unmistakable dilation of the pupil on the ganglion-free side. Removal of the ganglion of the sympathetic had rendered the pupil on that side far more sensitive to epinephrin. Stewart, Rogoff and Gibson found that this characteristic response was obtained when epinephrin was injected into the blood stream and was not obtained when the splanchnic was stimulated after the suprarenals had been removed, or when the circulation was interfered with in such a way that epinephrin could not reach the eye. The latent period for liberation of epinephrin from the suprarenals

4. Lewis, J. H.: Presence of Epinephrin in Human Fetal Adrenals, Jour. Biol. Chem., 1916, xxiv, 249.

5. Moore, B., and Purinton, C. O.: Am. Jour. Physiol., 1900, iv, 57; cited by Lewis.

6. Svehla: Arch. f. exper. Path. u. Pharmakol., xliii, 321; cited by Lewis.

7. Folin, Cannon and Denis: Jour. Biol. Chem., 1912-1913, xiii, 477; cited by Lewis.

8. Cannata, S.: Sulla presenza di adrenalina, nel sangue del neonato, Pediatria, 1915, Series 2, xxiii, 244.

9. Fulk, M. E., and Macleod, J. J. R.: Evidence That the Active Principle of the Retroperitoneal Chromaphil Tissue Has the Same Physiological Action as the Active Principle of the Suprarenal Glands. Am. Jour. Physiol., 1916, xl, 21.

10. Stewart, G. N., Rogoff, J. M., and Gibson, F. S.: The Liberation of Epinephrin from the Adrenal Glands by Stimulation of the Splenic Nerves and by Massage, Jour. Pharmacol. and Exper. Therap., 1916, viii, 205.

was exceedingly short, since the eye response seemed to occur at the same interval (a fraction of a second) whether the splanchnic nerve was stimulated or epinephrin injected into the renal vein. Massage of the suprarenal produced a similar eye response to that obtained by splanchnic stimulation. It was not found possible to exhaust the epinephrin supply in the suprarenals by fright, or morphin administration to such an extent that the characteristic effect on the eye could not be produced by splanchnic stimulation.

Hartmann[11] found that dilute solutions of epinephrin, for example, 1 to 100,000, caused a fall in blood pressure in the peripheral vessels, even after the latter had undergone dilatation as a result of hemorrhage, but that the same concentration of epinephrin produced a constriction of the splanchnic vessels.

Other investigators have previously reported dual action of epinephrin in dilute as compared with stronger concentration. Brodie and Cullis,[12] for example, found that minute concentrations produced constriction of the coronaries of animals, while stronger concentrations caused dilatation.

Hoskins[13] has conducted feeding experiments on white rats with desiccated suprarenal gland. The animals numbered forty-five, twenty-six serving as controls. Controls and experimental rats were of the same litters. The feedings were kept up from two to nine weeks. Hoskins found that the testes of the suprarenal fed animals showed definite hypertrophy, in accordance with the clinical evidence that the suprarenal cortex exerts a stimulating influence on the growth of the testes. No other effects of the suprarenal feeding were found. There were no disturbances in the growth or development of the rats.

Stilling,[14] in 1888, discovered that when one suprarenal is removed, the remaining gland undergoes compensatory hypertrophy and that it is the cortical and not the medullary portion which is affected. Biedl[15] in 1899 demonstrated by extirpation experiments in fish that the cortical and not the medullary element is essential to life. Crowe and Wislocki[16] have now found that after partial extirpation of the suprarenal, the part of the cortex which is left undergoes hyper-

11. Hartman, F. A.: The Differential Effects of Adrenin on Splanchnic and Peripheral Arteries, Am. Jour. Physiol., 1915, xxxviii, 438.

12. Brodie and Cullis: Jour. Physiol., 1911-1912, xliii, 313.

13. Hoskins, R. G.: The Effects of Suprarenal Feeding, Arch. Int. Med., 1916, xvii, 584.

14. Stilling, H.: Rev. de Méd., 1888, T9, 459; cited by Crowe and Wislocki.

15. Biedl, A.: Innere Sekretion, ihre physiologischen Grundlagen und ihre Bedeutung fur die Pathologie, 1913.

16. Crowe, S. J., and Wislocki, G. B.: Experimental Observations on the Suprarenal Glands with Especial Reference to the Functions of Their Interrenal Portions, Bull. Johns Hopkins Hosp., 1914, xxv, 287.

trophy, chiefly in the fascicular zone, while the medullary portion shows no change, either gross or microscopical. After almost total removal of both suprarenals, the animals developed subnormal temperature, frequent convulsions, and entered into a condition analogous to shock. If recovery occurred, it was gradual, but ultimately became complete. Although they found that an autoplastic transplant of suprarenal might take, the cortical cells surviving while the medullary cells died, such a transplant appeared to have no functional value. The authors had one dog under observation for a year after reduction of the suprarenals to a minute rest, which promptly died with the symptoms mentioned when this rest was removed. The following experiment is particularly instructive. On Nov. 13, 1912, Crowe and Wislicki removed from a dog nine-tenths of the right and one week later the entire left suprarenal. The dog survived. Six months later they ligated the vessels supplying the small piece of the right suprarenal which had been left. The ligation was followed by convulsions, subnormal temperature, etc. The animal surviving, on May 14, 1913, one-third of the rest was removed. Death then occurred in twenty-four hours after characteristic symptoms. The hypertrophy of the cortical portion of the rest was extreme, while the medullary portion showed no hypertrophy.

Elliott[17] has made an extensive study of human suprarenals in health and disease. Among the numerous observations which he has made the following are of particular interest: The lipoids of the suprarenal, which are normally found in the cortex, are stored and consumed under conditions entirely different from those which govern the storage and consumption of the body fat; for example, while the body fat disappears in starvation, the cortical lipoid of the suprarenal persists. The cortical lipoid vanishes rapidly, however, during acute infections and is diminished in chronic infections and anemias. The lipoid content of the cortex and the epinephrin content of the medulla have no relation whatsoever to each other. Elliott suggests that the function of the cortex may be to maintain the cholesterin ester content of the blood, which it is known becomes diminished under the same conditions as those under which the cortical lipoid of the suprarenal becomes diminished. He suggests also that the cortex of the suprarenal has a relationship to growth and sexual maturation. He points out the interesting fact that, morphologically, the cortical cells of the suprarenal are akin to the interstitial cells of the testis.

Turning to the consideration of the medullary function of the suprarenal, he finds no evidence that high blood pressure depends on an increased epinephrin secretion. The epinephrin content is at its

17. Elliott, T. R.: Pathological Changes in the Adrenal Glands, Quart. Jour. Med., 1914-1915, viii, 47.

lowest "in the afebrile acute cardiac failure associated with mental distress in the struggle to live," but is not lower or higher in diseases accompanied by high blood pressure than in others.

Jump, Beates and Babcock[18] have collected from the literature seventeen cases of precocious sexual development associated with suprarenal tumor, all of which were confirmed by necropsy. It is interesting to note that fourteen of the seventeen patients were girls. In all the cases there was an overgrowth of pubic hair; in fourteen of them hair was present on the face; and in five there was axillary hair. Overgrowth of the body as a whole occurred in all. Precocious menstruation and breast development appeared in only one. The majority of the children showed diminished intelligence, but some appeared to be unusually bright. There seemed to be a tendency toward the assumption of the masculine type of sexual development in all the females and an exaggeration of the normal in the sexual development of the males. The tumor always involved the suprarenal cortex.

Baldwin[19] adds another case, a boy 5 years old, whose face was like that of a man and had been shaved for some time. The father thought that the premature sexual development had been evident at about the 18th month. Hair on the pubis and face appeared at 3, and at that time it was noticed the voice was like that of a man. The genitalia resembled those of the adult, except that the testes were small and not completely descended. Necropsy showed a large hypernephroma of one suprarenal and a small one of the other. The other organs of internal secretion were normal.

Van der Bergh reports still another case of hypernephroma of the suprarenal in a girl of 3 years with somatic changes analogous to those just described. The girl was from 4 to 5 inches taller than the average, and her general aspect and the appearance of her genital organs suggested the adult state. There was no indication of pineal or hypophysial tumor. The hypernephroma was removed and weighed 2,000 gm. Van der Bergh reviews the literature. The ages in his group of cases ranged from 14 months to 14 years; two girls of 5 and 9 years had beards; extreme obesity occurred in several cases.

THE CAROTID "GLAND"[20]

Luschka, in 1862, gave the first accurate histologic description of the carotid bodies and expressed the view that they were glands and

18. Jump, H. D., Beates, H., Jr., and Babcock, W. W.: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, Am. Jour. Med. Sc., 1914, cxlvii, 568.

19. Baldwin, J. F.: Adrenal Precocity; Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, Jour. Am. Med. Assn., 1914, lxiii, 2286.

20. Betke's article, on which this review is based, contains a complete bibliography and discussion of the entire subject.

not nervous tissue. Arnold, on the other hand, considered them actually to be blood vessels which branched and developed high epithelium in such a manner as to cause histologic resemblance to glandular tissue.

Embryologists have derived the carotid bodies from the third branchial cleft (from the thymus), from the thyroid anlage and from the sheath of the carotid vessels. Kohn first recognized that the carotid bodies were composed of chromaffin tissue, and consequently their relationship to the sympathetic system.

In man the carotid bodies are two minute structures, 5 to 7 microns in length by 2.5 to 4 microns in breadth, each of which lies on the medial side of the corresponding common carotid artery at its bifurcation.

The only clinical importance of the carotid bodies is that they occasionally give rise to tumors, more than thirty-nine cases of which have been reported, the youngest in a 16-year-old girl. These tumors have never been accompanied by constitutional disturbance.

The function of the bodies has been investigated by Vassale, Frugoni, Schmidt and Betke. Frugoni injected extracts into animals and obtained results which are now recognized as the effects of tissue extract, such as fall in blood pressure, collapse, etc. His conclusion was that the carotid bodies were organs of internal secretion, having a depressing influence on blood pressure.

Schmidt excised the carotid bodies in two stages by first removing the bifurcating portion of the carotid artery on one side with its carotid body and subsequently the carotid artery and body of the other side. Since he obtained no symptoms or pathologic changes as a result of his extirpation experiments, he concluded that the bodies are functionless rudiments.

Betke[21] repeated Schmidt's experiments on dogs and cats. He noted no changes for from four to eight weeks, but after that latent period had elapsed, there occurred retardation in growth, increasing weakness and cachexia, which led after a few months to death. The necropsies showed no cause of death in either abdomen or thorax. The chief pathologic changes were found in the skeleton and the spleen. The skeleton showed both microscopic and macroscopic evidences of rickets; the spleen showed a disappearance of the follicles, in some instances accompanied by an increase in the connective tissue; large cells of the megalokaryocyte type were numerous. The bone marrow was characterized by atrophy of the marrow cells.

Betke concluded that the carotid bodies are essential to life and

21. Betke: Experimentelle Untersuchungen über die physiologische Bedeutung der Glandula carotica, Beitr. z. klin. Chir., 1915, xcv, 343.

are, therefore, to be considered among the most important organs of internal secretion, belonging to the group which presides particularly over the growth of bone, and that they probably have some influence on blood formation.

It is interesting to note that Betke's experiments were published from Rehn's clinic in Frankfort, where the experiments of Klose and of Flesch on the thymus were also performed. All three investigators, the one extirpating the carotid bodies, the other two the thymus, obtained almost identical results. The coincidence in the results of such widely different experiments suggests that some common factor, unrelated to the removal of either thymus or carotid bodies, may have been operative, such as infection, confinement, poor care, or improper food, or a combination of these, giving rise to illness characterized by the gradual development of rickets and ending finally in death, making its appearance among those animals subjected to operation.

In any event, it is difficult to imagine that the carotid bodies can be essential to life, if it is true that they are merely aggregations of chromaffin tissue, when it is considered that chromaffin tissue is widely distributed in the body and even the comparatively immense mass of chromaffin tissue comprising the medullary portions of the adrenal glands is not essential to life.[22] Further proof must be offered before Betke's work can be accepted.

THE PARATHYROIDS

Not much important literature on the subject of the parathyroid glands has appeared during the past two years.

Thimm[23] points out that the presence of more than two parathyroids on a side does not mean that the anlagen were more than their usual number.

In almost all the higher mammals parathyroid III is the lowermost, that is, the more caudally situated of the two parathyroids, but since it takes origin from the third pharyngeal pouch, while parathyroid IV, as its name indicates, develops from the fourth pharyngeal pouch, its original position in the embryo was above (cephalad to) that of parathyroid IV. The explanation of the more caudal position of parathyroid III lies in the fact that during its development it descends from its place of origin at the third pharyngeal pouch in company with the thymus cord, also derived from the third pharyngeal pouch, in the course of the migration of the latter downward (caudalward) toward the thorax, and comes to rest in most species of animals near the lower

22. Biedl: Innere Sekretion, 1916.

23. Thimm, L.: Zur Kenntnis der Epithelkörperchen (Glandulae parathyreoideae), Arch. f. Kinderh., 1914, lxiii, 321.

pole of the thyroid, but in the rabbit descends farther, so as to lie often considerably below the thyroid, usually in the substance of the thymus gland. Parathyroid III is the larger and more constant of the two parathyroids.

To return now to Thimm's paper: When there are more than two parathyroids on a side, the meaning is that parathyroid III was drawn out during its fetal descent into a thin cord, which became either actually broken up into a number of fragments, each forming a separate parathyroid, or else so thinned in places as to give the appearance of several separate parathyroids, when in reality thin strands of parathyroid tissue (often so minute as to be capable of demonstration only on microscopic examination of serial sections) joined them together in a continuous chain.

There is rarely, if ever, more than one parathyroid derived from the fourth pharyngeal pouch on a side, and not always even one. For example, in the guinea-pig parathyroid[24] IV is frequently absent or rudimentary.

Fulci and Giannuzzi[25] extirpated some of the parathyroids in rabbits and studied the parathyroid tissue that remained for resulting histologic changes. Though the rabbits died five or six days after the operation, with the symptoms of parathyroid tetany, the investigators were able to detect in the parathyroid rests signs which they interpreted as regeneration. Epithelial strands passed from the main mass or masses of parathyroid tissue into the surrounding connective tissue, like the extensions from a neoplasm; some of the cells of the strands were undergoing division and young blood vessels were visible. They observed the same signs of regeneration in the parathyroid tissue of older animals after incomplete parathyroidectomy, as well as in the parathyroids of younger animals.

Thimm's work suggests that Fulci and Giannuzzi might have mistaken the strands connecting separate masses of parathyroid tissue for regenerating parathyroid. In any event, their work is not very convincing.

Jackson[26] investigated the effects of inanition on the parathyroids of rats. The parathyroids did not appear to be reduced in young rats by inanition, but in older rats to an extent commensurate with the loss

24. Ruben, R.: Zur Entwicklung der Thymus und der Parathyreoidea beim Meerschweinchen, Anat. Anz., Jena, 1911, xxxix, 571.

25. Fulci, F., and Giannuzzi, A.: Ueber die Regenerationsfähigkeit der Parathyreoidea (Vorläufige Mitteilung), Centralbl. f. allg. Path. u. path. Anat., 1915, xxvi, 97.

26. Jackson, C. M.: Effects of Inanition on the Structure of the Thyroid and Parathyroid Glands of the Albino Rat, Anat. Rec., 1916, x, 208.

of body weight. He found that the parathyroid is less apt to develop structural changes during starvation than the thyroid and that normal variations in the histology of the parathyroids are less marked than in the thyroids.

By far the most important experimental work on the parathyroids which has appeared during the past two years is that of MacCallum, Lambert and Vogel.[27] These investigators performed experiments on dogs to show in a new way that the increased excitability of the peripheral nerves in tetany is caused by the lowered calcium content of the blood. The calcium content of defibrinated dog's blood was reduced in their experiments by means of the dialysis method of Abel, Rowntree and Turner; that is, the blood was passed repeatedly through a series of celloidin tubes immersed in a fluid which had the same inorganic composition as dog's blood, with the exception that calcium was absent. By dialyzing dog's blood against this fluid the calcium content of the blood was reduced, for example, from 0.0364 gm. to 0.0284 gm. per liter. But the dog's blood could not be rendered calcium free by this method.

When the defibrinated blood with its reduced calcium content was perfused through the isolated extremity of a dog, increased excitability of the nerves was obtained, as determined by the galvanic current. But when the calcium-reduced blood was introduced into a living animal, that is, substituted for the normal blood of the animal, no such lowering of the excitability of the peripheral nerves took place, for the apparent reason that the calcium of the tissues of the dog passed over so readily into the calcium-reduced blood as speedily to make up the previously created deficiency in the latter. It is a well-known fact that the introduction of normal blood into an animal suffering from tetany stops the symptoms of tetany for a time. But when calcium-reduced blood was introduced into an animal suffering from parathyroid tetany no improvement of the symptoms resulted, thus demonstrating again the dependence of the symptoms of tetany on the lowered calcium content of the blood.

The authors advance the hypothesis that the function of the parathyroid may be to convert the "nondialyzable calcium into a dialyzable form, which latter is essential for the control of the excitability of the nerves, but which is lost in the excreta and not newly formed in the absence of parathyroid secretion."

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27. MacCallum, W. G., Lambert, R. A., and Vogel, K. M.: The Removal of Calcium from the Blood by Dialysis in the Study of Tetany, Jour. Exper. Med., 1914, xx, 149.

THE PINEAL GLAND[28]

The pineal gland was selected by Descartes (1628) as the probable seat of the soul, on account of its central position in the brain and its proximity to the ventricles. It has been considered as a possible organ of internal secretion only since other structures of doubtful significance to the body have been found to be glands of internal secretion of vital importance. Embryologically, the pineal gland is the vestigeal remnant of the pineal eye of the reptiles and certain other lower forms.

Gutzeit[29] in 1896 reported a case of teratoma of the pineal in a 7-year-old boy with precocious sexual development. Oestreich and Slawyk[30] in 1899 reported another case and almost simultaneously Ogle[31] reported a third case of pineal teratoma, both of them in boys less than 7 years old showing precocious sexual development. By 1907 enough case reports of tumor of the pineal had accumulated in the literature for Marburg[32] to collect forty-one, including his own. Although only two of Marburg's forty-one cases of pineal tumor showed precocious sexual development, and only a very small number a bodily development exceeding the normal, and in spite of the fact that no experimental work has been done on the pineal which could be used as a basis for speculation (Dandy), Marburg enunciated three clinical syndromes. Hyperpinealism, according to Marburg, gave rise to adiposity; apinealism, to cachexia; and hypopinealism to precocity of sexual development and to hypertropic conditions of the genitalia.

Since Marburg's publication other cases of pineal tumor have been added to the list, bringing the total number, according to Horrax, to seventy. But in only two of these more recently reported cases have there been the symptoms of precocious sexual development, one, the case of von Frank-Hochwart[33] (1909) in a boy 5½ years old, the other, Horrax's own case (1916). Horrax has reported, in addition to the case of pineal tumor just mentioned which was made certain by necropsy, two additional cases thought to be pineal tumor on purely clinical grounds, but on such slim evidence as to make consideration of them unnecessary.

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28. A review of the entire subject by Kidd up to 1913 will be found in the Review of Neurology and Psychiatry, xi, 1-24 and 55-75. Marburg, Ergebn. d. inn. Med. u. Kinderh., 1913, x, 146, gives a complete discussion of the subject in its clinical aspects. Horrax: Arch. Int. Med., brings the bibliography up to date and gives an excellent résumé of the literature.

29. Gutzeit: Ein Teratom der Zirbeldrüse, Diss. Königsberg; cited by Kidd.

30. Oestreich and Slawyk: Virchows Arch. f. path. Anat., clvii, 475; cited by Kidd.

31. Ogle, Trans. Path. Soc., Lond., Vol. 50, p. 6.

32. Marburg: Wein. med. Wchnschr., 1908, xlviii; Arbeiten a. d. Wiener neurol. Inst., 1906, xiii, 288; Ibid., 1909, xvii, 217; Ergebn. d. inn. Med. u. Kinderh., 1913, x, 146.

33. Frankl-Hochwart: Deutsch. Ztschr. f. Nervenh., 1909, xx, 455; cited by Horrax.

Horrax'[34] authenticated case of pineal tumor was that of a boy aged 12 years, who had always been well except for asthmatic attacks until three and one-half months before his admission to the Brigham Hospital. There they noted that the patient was a lean boy, weighing 97 pounds, with some pigmentation of the skin, unequal pupils, choked disk, diplopia on looking to the right, suggestive Romberg, positive Kernig's sign, some stiffness of the neck and ataxia of the left arm. The symptoms, which had been observed during the three and one-half months prior to his admission to the hospital, were dilated and unequal pupils, a staring expression, blurred vision, headache, nausea and vomiting. The case was thought probably to be tuberculous meningitis. When, however, the necropsy revealed pineal tumor, certain other symptoms which apparently had not been sufficiently prominent to attract due attention were recalled. The boy, though lean, had gained 40 pounds[35] during the year preceding his acute illness; the pigmentation of the skin was distributed differently from that of sunburn; the genitalia were developed in advance of the age; there was a little pubic hair and the down on his face was in excess of the normal.

The important fact which the clinical study of tumors of the pineal gland brings out is that out of a total of seventy cases reported in the literature, symptoms of precocious sexual development appear in only five, and excessive growth in not more than seven. The study of case reports of pineal tumor, therefore, raises the inquiry whether the pineal gland has in reality anything to do with either sexual or physical development; in other words, whether precocious sexual development or growth occurring in cases of pineal tumor can not be explained by pressure effects on neighboring structures (the hypophysis?).

The most important symptoms of pineal tumor from the standpoint of diagnosis are the focal symptoms produced by the pressure of the tumor against the corpora quadrigemina and underlying structures, with resulting rather characteristic involvements in the distributions of the oculomotor nerves on both sides, and vertigo. The focal symptoms are usually accompanied by general symptoms of tumor. It may be said that if precocious sexual or physical development is present in a given case, unaccompanied by any focal symptoms pointing definitely to the pineal, it is probable that the cause lies elsewhere than in the pineal gland.

Cysts are the most frequent form of pineal tumor and next to cysts, teratomas. All five cases of pineal tumor showing precocious sexual development have been teratomas of the pineal. Hemorrhage into the

34. Horrax, Gilbert: Studies on the Pineal Gland. I. Experimental Observations, Arch. Int. Med., 1916, xvii, 607.

35. He weighed 114 pounds at the beginning of his illness.

pineal and abscess of the pineal have been reported, and also tuberculous and syphilitic involvements.

The experimental attempts to determine the existence of pineal function have followed the usual lines employed in the determination of the function of organs of internal secretion, namely, feeding and injection experiments and extirpation of the gland.

Extirpation of the pineal gland has been performed by Sarteschi[36] in 1910 (rabbits) and in 1913 (puppies and guinea-pigs); by Biedl[37] in 1910 (dogs); by Exner and Boese[38] in 1910 (rabbits); and by Foà[39] in 1912 and 1914 (chickens). Sarteschi had very few survivals from his experiments. One puppy gained more rapidly in weight than the control puppy and at autopsy it was found that the testes were larger than those of the control. Biedl's three surviving dogs[40] showed no effects. Exner and Boese's six surviving rabbits remained normal. Foà succeeded in his first set of experiments in bringing three pinealectomized cocks and twelve hens to maturity. The pinealectomized cocks crowed and were sexually active from forty-two to seventy-nine days before their controls, and developed hypertrophied combs and testes. In his second set of experiments two male and five female chickens survived. The two males developed in exactly the same way as the males of the first set of experiments. But the females in both sets of experiments remained entirely normal. Foà also removed the pineal gland from a few rats, with indefinite results very similar to those obtained by Horrax.

Adler, attracted by the experiments of Foà, investigated pineal function in the frog. The frog larva seemed to be particularly adapted for demonstration of the effects of extirpation of the pineal. For if the pineal regulates in some special way growth and development, its activity should be intense at the period of metamorphosis from the larval state, and consequently the changes produced by its removal should become very evident as the period of metamorphosis falls due. In the second place the phenomenon of sudden transition from tadpole to frog, at about the tenth to the thirteenth week, afforded a splendid means of measurement of any influence on the development and growth of the animal.

Adler[41] pinealectomized by means of the thermocautery 850 tad-

36. Sarteschi, U.: Folia Neurobiologia, Vol. iv, No. 6; cited by Kidd.
37. Biedl, A.: Innere Sekretion, 1913, p. 194.
38. Exner and Boese: Deutsch. Ztschr. f. Chir., 1910, cvii, 182; München. med. Wchnschr., 1911, i, 154; Neurol. Centralbl., 1910, 754.
39. Foà, C.: Arch. ital. de biol., 1912, lvii, 233; Ibid., 1914, lxi, 79; Pathologica, iv, 445.
40. Biedl's dogs were fully grown at the time of operation.
41. Adler: Extirpation der Epiphyse, Arch. f. Entwicklungsch. d. Organ., 1914, xl, 1.

poles, averaging 21 mm. in length. However, a very small number of them survived the operations and the subsequent period of observation. His operative frogs showed no differences in growth or development, which he felt justified in referring to the removal of the pineal. When he killed the surviving animals two months after the pinealectomy, he was unable to find any changes in thyroid, hypophysis, thymus, or in the testis. He concluded, therefore, that the pineal does not exercise in the frog the functions which were indicated by Foà's experiments in the fowl.

Dandy[42] (1915) was the first to devise a satisfactory experimental method for removal of the pineal gland in dogs. The methods used by the investigators already mentioned were accompanied by a high mortality, due to hemorrhage from the veins of Galen, which are in close proximity to the pineal gland. Dandy's method depends on an exposure of the pineal by incision through the corpus callosum. He used dogs varying in age from 10 days to 3 weeks, the exact number of which are not stated in his publication. One of his animals was alive fifteen months after the operation; one died of distemper one year afterward; and several survived three to eight months, dying of some condition entirely unrelated to the pineal. Dandy's experiments were hampered by the distemper and mange. He was unable to detect any change in his animals in their sexual or physical development, or in the histology of any of the organs, including the organs of internal secretion. He concluded that the pineal is not essential to life and that removal of the gland in dogs furnishes no evidence that it possesses a function.

The most recent pineal extirpations are those of Horrax[34] in guinea-pigs and rats. Out of a large number of guinea-pigs Horrax succeeded in removing the pineal completely in fifteen males and twenty females, which were able to survive the operation. His animals were 2 days to 7 weeks old at the time of the operation, and were kept under observation for periods varying from seven and one-half to fourteen weeks. He controlled his operative animals chiefly but not entirely from the same litters aud performed on the controls sham operations, stopping short of removal of the gland. Horrax found that loss of the pineal was not followed by any change in the weight curve. He did find, however, that the testes of the male animals of his operative series outweighed those of the controls, averaging 12.8 gm. as opposed to 9.9 gm., the average weight of the testes of the controls. Between the ninth and eleventh weeks minor histologic changes were found; but in younger animals none were present, and in older animals

42. Dandy, W. E.: Extirpation of the Pineal Body, Jour. Exper. Med., 1915, xxii, 2.

the changes, if formerly present, had disappeared. The changes noted in the period between the ninth and eleventh weeks were larger tubules and more signs of spermatogenesis than in the testes of the control animals. The seminal vesicles of the operative guinea-pigs also appeared to be the more distended and to contain a colloid substance in greater abundance. The female animals in Horrax' experiments seem to have been essentially unaffected, although he thought he could discern a tendency toward earlier conception.

Horrax' pinealectomies in rats showed really nothing except that the operation was feasible in that species of animals, for his experimental material was killed off in large part by an epidemic.

Horrax draws two conclusions from his experiments, that the loss of the pineal hastens the growth and maturation of the testes and tends to accelerate sexual maturity in the females.

Howell,[43] 1908, Dixon and Halliburton,[43] 1909, Jordan and Eyster,[43] 1911, Ott and Scott,[43] 1912, injected pineal extract into animals, obtaining on the whole negative results. Horrax, using pineals from young calves and sheep to make his extract, obtained a fall in blood pressure. McCord[44] also obtained a drop in blood pressure by injection of pineal extract into animals, and in some instances even death. Both investigators attributed the fall to the physiologic action of the internal secretion of the pineal gland.

Dana and Berkeley[45] have performed feeding experiments on young guinea-pigs, kittens and rabbits. They found that the animals fed with pineal gained weight more rapidly than the control animals. They then fed pineal glands to defective children, including mongolian idiots, and found that their mental progress was more rapid, though they did not gain in weight so rapidly as the control children.

The most numerous feeding experiments have been done by McCord.[44] He fed powdered extract of pineals taken from animals of different ages to guinea-pigs, puppies, adult dogs and chicks with remarkable results. He found that chickens fed with the extract of the pineals of young animals gained in weight more rapidly than the control chickens, but that when they were fed extract from pineals of mature cattle, they gained no more rapidly than the controls. In his feeding experiments on guinea-pigs he found a symmetrical overgrowth of the pineal-fed guinea-pig and also an acceleration of sexual

43. For references to the work of these investigators consult Kidd or Horrax.

44. McCord, C. P.: The Pineal Gland, Interstate Med. Jour., 1915, xxii, 354; The Pineal Gland in Relation to Somatic, Sexual and Mental Development, Jour. Am. Med. Assn., 1915, lxv, 517.

45. Dana, C. L., and Berkeley: The Functions of the Pineal Gland, Med. Rec., New York, 1913, lxxxiii, 835; cited by Horrax. Berkeley, W. N.: The Use of Pineal Gland in the Treatment of Certain Classes of Defective Children, Med. Rec. New York, 1914, lxxxv, 513; cited by Horrax.

maturity, as demonstrated by the fact that with but two exceptions young guinea-pigs were born to the pineal-fed females left to breed naturally with pineal-fed males earlier than young were born to the control females bred to control males. McCord's experiments on puppies were rendered of little value because of an epidemic of distemper. Nevertheless, he thought he could detect more intelligence in the pineal-fed dogs than in the controls, as well as increased growth. He remarks that when his experiments were finished only the pineal-fed dogs were in demand as pets.

It seems probable that a mass of experimental literature of a conflicting nature will develop about the pineal body, like that which has sprung up around the thymus and the spleen. It can now be said that the experimental work on the pineal up to the present time has failed to prove that it possesses a function. The results of Foà, which were negative in the pullets and positive only in a few cocks, cannot be regarded as in any way final. The changes which Horrax obtained were so slight as to make it seem remarkable he should have regarded his experiments as positive. If the extraordinary results which McCord obtained by feeding pineal were actually caused by the active principle of the gland, the extirpation experience of Dandy and Horrax ought to have brought overwhelming evidence of pineal function and clinical literature to abound with examples of pineal disease.

THE PITUITARY

Keeton and Becht[46] found that direct electrical stimulation of the hypophysis caused an increase in the reducing substance of the blood, while stimulation of the brain in front of and behind the hypophysis failed to produce any increase in the reducing substance. The increase did not take place in dogs whose splanchnic nerves had been cut—a finding not in accord with the theory held by Cushing and others that it is the hormone discharged by the hypophysis into the blood which causes mobilization of the glycogen.

Dandy and Goetsch[47] have shown that fibers from the sympathetic are sent to the pituitary body. By stimulating the cervical sympathetic ganglia Shamoff[48] obtained glycosuria and diuresis in eight out of fifteen animals tested. All nervous pathways from the stimulated ganglion to the kidneys had been cut. Shamoff, therefore, arrived at the opposite conclusion from Keeton and Becht, namely, that it was the secretion of the hypophysis thrown out into the blood stream as a

46. Keeton, R. W., and Becht, F. C.: The Stimulation of the Hypophysis in Dogs, Am. Jour. Physiol., 1915, xxxix, 109.

47. Dandy and Goetsch: Am. Jour. Anat., 1910, xi, 137; cited by Shamoff.

48. Shamoff, V. N.: Concerning the Action of Various Pituitary Extracts on Isolated Intestinal Loop, Am. Jour. Physiol., 1915-1916, xxxix, 268.

result of stimulation of the sympathetic which produced glycosuria and diuresis, especially in view of the fact that the response obtained was a typical pituitary response, as was indicated by the combination of increased blood pressure, glycosuria and polyuria.

Weed and Cushing[48] determined that extract of the posterior lobe of the hypophysis introduced intravenously into animals caused an increase in the rate of production of the cerebrospinal fluid. The increase obtained appeared to be independent of respiratory or hemodynamic influences. The authors consequently thought that it was due to the specific action of some substance in the posterior lobe of the hypophysis on the choroid plexus, stimulating it to increased secretory activity.

McCord[50] found that the pituitary in eight-year-old bovine fetuses showed the presence of the active principle as determined by the method of Dale and Laidlow.[51] McCord believes the active principle of the pituitary is present in fetal life as early as the gland is capable of macroscopic recognition.

Lewis[52] found that the quantity of pressor substance contained in the hypophysis of the pig fetus of 175 mm. was sufficient to indicate that a pig fetus of this size is independent of its mother's hypophysial secretion. Lewis discovered evidences of the pressor substance in the hypophysis of pig fetuses 125 mm. long.

Fenger[53] attempted to determine by the use of the uterus strip method of Fraenkel whether a seasonal variation in the secretory activity of the posterior lobe of the hypophysis could be demonstrated, but was unable to find any difference in the extracts from summer and winter glands.

The literature of the past two years contains reports of a number of experiments in pituitary feeding which have given quite discordant results.

Pearl and Surface[54] obtained no evidence that the hypophysis activates the resting ovary of the hen.

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49. Weed, L. H., and Cushing, H.: Studies on the Cerebrospinal Fluid. VIII. The Effect of Pituitary Extract on the Secretion (Choroidorrhea), Am. Jour. Physiol., 1914-1915, xxxvi, 77.

50. McCord, C. P.: The Occurrence of Pituitrin and Epinephrin in Fetal Pituitary and Suprarenal Glands, Jour. Biol. Chem., 1915, xxiii, 435.

51. Dale, H. H., and Laidlaw, P. P.: Jour. Pharm. and Exper. Therap., 1912-1913, iv, 75; cited by McCord.

52. Lewis, D.: The Appearance of Pressor Substance in the Fetal Hypophysis, Jour. Exper. Med., 1916, xxiii, 677.

53. Fenger, F.: On the Composition and Physiological Activity of the Pituitary Body, Jour. Biol. Chem., 1915, xxi, 283.

54. Pearl, R., and Surface, F. M.: Studies on the Physiology of Reproduction in the Domestic Fowl. XIII. On the Failure of Extract of Pituitary Body (Anterior Lobe) to Activate the Resting Ovary, Jour. Biol. Chem., 1915, xxi, 95.

L. M. Clark[55] found, on the other hand, that feeding of the pituitary gland (the anterior lobe) of young cattle to hens raised the egg production curve at a time when the latter was normally on the decline. The effect was noticed four days after feeding was begun and lasted for a number of days after it had been stopped. He observed, further, that a greater percentage of eggs hatched when both parents had received pituitary feeding than when no pituitary was used.

Pearl,[56] who also fed desiccated substance of anterior lobe of hypophysis to hens at the period of decline in egg production, could find no evidence that it produced any effect. He came to the conclusion that feeding of the pituitary to growing pullets does not bring about earlier activation of the ovary. The feeding of the anterior lobe to chicks, however, produced a retardation in growth.

Robertson[57] studied the effects of pituitary feeding on the growth of mice. The administration of 0.125 gm. per day of anterior lobe pituitary tissue to mice, begun in the fourth week, led to retardation of growth during the earlier portion of what Robertson terms "the third growth cycle," that is, between the sixth and twentieth weeks; but from the twentieth to the sixtieth week, in the latter part of "the third growth cycle," to an acceleration of growth, so that the pituitary-fed mice caught up to and surpassed the controls. Robertson further observed that pituitary-fed animals from the thirtieth week onward appeared more compactly built than the controls. Though "weight for weight they were smaller, size for size they were heavier." He also observed that the pituitary-fed animals showed marked belligerency.

Robertson[58] thinks he has isolated the active principle of the anterior lobe of the pituitary, which affects growth, giving it the name "tethelin." The effects on mice obtained by its administration were identical with those which followed the administration of the entire gland. It is prepared by extracting the dried tissue of the anterior lobe of the pituitary with boiling alcohol and precipitating with ether.

Robertson[59] investigated the effects of extracts of the anterior lobe

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55. Clark, L. N.: The Effect of Pituitary Substance on the Egg Production of the Domestic Fowl, Jour. Biol. Chem., 1915, xxii, 485.

56. Pearl, R.: Studies on the Physiology of Reproduction in the Domestic Fowl, Jour. Physiol. Chem., 1916, xxiv, 123.

57. Robertson, T. B.: Experimental Studies on Growth. III. The Influence of the Anterior Lobe of the Pituitary Body on the Growth of the White Mouse, Jour. Biol. Chem., 1916, xxiv, 385.

58. Robertson, T. B.: On the Isolation and Properties of the Anterior Lobe of the Pituitary Body, Jour. Biol. Chem., 1916, xxiv, 409.

59. Robertson, T. B., and Burnett, T. C.: The Influence of the Anterior Lobe of the Pituitary Body on the Growth of Carcinomata (Preliminary Communication), Proc. Soc. Exper. Biol. and Med., 1914, xii, 68; Jour. Exper. Med., 1915, xxi, 280.

of the hypophysis on the growth of carcinomas inoculated into rats. He found that emulsion of the anterior lobe of the ox pituitary markedly increased the rate of growth of the primary tumor and that small tumors were affected even more than large tumors. But the acceleration in growth was evidenced only at a certain stage in the growth of the tumor, subsequent to the twentieth day after inoculation.

Goetsch[60] also has made feeding experiments with the pituitary gland to determine the effects on growth and sexual development. He used white rats, choosing stock of known pedigree, in order to reduce normal variation in his material to the lowest possible point. He conducted separate experiments, using the dried, powdered extract of the entire hypophyses and of the anterior and posterior lobes, respectively.

When dried extract of the entire gland was fed to young rats in excessive doses (0.1 gm. daily), it caused failure to gain in weight, loss of appetite, diarrhea, muscular weakness and tremor. These symptoms Goetsch attributed to the activity of the posterior lobe element. When whole gland was fed in smaller dosage, it caused within from twenty-five to forty days a more rapid growth and development, larger nipples in the females, and a more coarse, harsher coat of hair than in controls fed on the same diet. Some of the controls received ovarian extract in the same dosage as that of the hypophysis. The influence of whole gland feeding on the sex glands of the female was to make the ovaries, tubes and cornua of the uterus larger and more vascular than those of the controls and maturity of the ovary to occur one or two months before the normal time. Maturity of the ovary was indicated by active ovulation and Graafian follicle formation. The effect of whole gland feeding on the genital organs of the male was the production of a more rapid growth and development of the testes, an earlier descent, precocious spermatogenesis occurring at a time when the testes of the controls were still immature.

The feeding of anterior lobe alone caused increased weight, greater and more vigorous body growth and an earlier and more active genital development, but without the diarrhea and nervous manifestations seen at the beginning of whole gland feeding. The period of sexual development was shortened by at least one month. That feedings of the anterior lobe produced earlier and greater sexual activity was demonstrated by the fact that a male and a female fed with anterior lobe over a period of from eight to nine months bred earlier and oftener than a control pair, producing two litters in seven months, while the control pair had no offspring. The effect of continued

60. Goetsch, E.: The Influence of Pituitary Feeding on Growth and Sexual Development. An Experimental Study, Bull. Johns Hopkins Hosp., 1916, xxvii, 29.

anterior lobe feeding on the sex glands held throughout the life of the animal and was greater, the longer had been the period of administration. Its stimulating effect on the parents was seen in the offspring in intrauterine development and during lactation; and when feeding of the offspring with anterior lobe was begun as soon as lactation from the hypophysial-fed mother had come to an end, the very maximal effects were produced.

Posterior lobe feeding did not stimulate growth or the development of the sex glands; in fact, it seemed to retard the development. In large doses it caused a diarrhea, with loss of weight.

It might be mentioned that ovarian extract, Goetsch found, had a stimulating influence on the sexual development of the female, but a retarding influence on that of the male.

Solem and Lommen[61] have found that injection of pituitary extract causes a decrease in the flow of saliva. In their opinion the decrease is brought about by the constricting action of pituitary extract on the arterioles of the salivary glands, which diminishes their blood supply and also by its specific inhibiting influence on the secretary nerves of the glands.

Simpson and Hill[62] have studied the effect of pituitary extract on milk production. Their conclusion is as follows:

> The administration of pituitary extract, by intravenous, intramuscular or subcutaneous injection, to a lactating animal leads to a marked increase in the quantity of milk secreted and also in its fat content. In the goat, if the injection be continued at intervals over a prolonged period—several months—immunity to its action on the mammary glands appears to be established both in regard to the amount of milk yielded and the percentage of fat it contains.

Livingston[63] castrated and spayed rabbits to determine any resulting alterations in the weight of the organs of internal secretion, in particular the hypophysis. He found that though hypertrophy of the hypophysis did not regularly follow spaying or castration, it usually occurred and was a commoner development in females than in males. On the other hand, he discovered that a constant relationship did exist between increase in body weight and hypertrophy of the hypophysis, that is, an increase in the size of the hypophysis was accompanied by increased rate of growth and vice versa. No effect on the suprarenals or thyroid could be detected.

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61. Solem, G. O., and Lommen, P. A.: The Influence of the Extract of the Posterior Lobe of the Hypophysis on the Secretion of Saliva, Am. Jour. Physiol., 1915, xxxviii, 339.

62. Simpson, S., and Hill, R. L.: The Effect of Repeated Injections of Pituitary Extract on Milk Secretions, Am. Jour. Physiol., 1914-1915, xxxvi, 347.

63. Livingston, A. E.: The Effect of Castration on the Weight of the Pituitary Body and Other Glands of Internal Secretion in the Rabbit, Am. Jour. Physiol., 1916, xl, 153.

Cushing and Goetsch[64] have made an interesting study of the organs of internal secretion in seven hibernating woodchucks. They found changes of a minor character in several of the organs of internal secretion, but the most definite changes in the hypophysis. The latter was reduced in size, and the cells of the pars anterior in some of the animals had lost their characteristic staining reactions to acid and basic dyes. After hibernation was over, the gland regained its normal size and the cells their normal staining properties and showed signs of division. Their conclusion is as follows:

> On the basis of these observations hibernation may be ascribed to a seasonal physiological wave of pluriglandular activity. The essential rôle may perhaps be ascribed to the pituitary body, not only for the reason that the most striking histological changes appear in this structure, but also because deprivation of the secretion of this gland alone of the entire ductless gland series produces a group of symptoms comparable to those of hibernation.

They base the conclusion just given on an analogy. Human beings with hypopituitarism have shown storage of fat, slow pulse and respiration, extreme somnolence and subnormal temperature. The hibernating animal shows exactly this same group of symptoms. The histologic changes in the hypophyses of both are similar. Since the alteration in the hypophysis appears to be the cause in the one, it must be the chief cause at least of the other. Cushing and Goetsch point out that the theory originated with two Italians, Salmon (1905) and Gemelli (1906), both of whom, however, had, in Cushing and Goetsch's opinion, an incorrect conception of the mode of activity of the hypophysis.

Their conclusion that hibernation is the result of a "wave of pluriglandular inactivity" with the hypophysis playing "the essential rôle" forms an attractive hypothesis.

Fry[65] has made histologic studies of the pituitary in eight cases of diabetes, two of myxedema, one of cystic goiter, one of Addison's disease and one of status lymphaticus. In the hypophysis of diabetes he found an increase in the chromophil cells, which appeared as adenomatous masses, evidences of conversion of chromophil cells into colloid and, in some instances, degenerative changes which were so extensive that few of the cellular elements in the anterior lobe remained. He believed these changes were not a part of a general reaction of the body tissues to the disease, but indicated that the hypophysis was primarily affected and consequently that it might be primarily concerned in the causation of diabetes. In the case of myxedema he

64. Cushing, H., and Goetsch, E.: Hibernation and the Pituitary Body, Jour. Exper. Med., 1915, xxii, 25.

65. Fry, H. J. B.: The Pituitary Gland in Diabetes Mellitus and Disorders of the Glands of Internal Secretion, Quart. Jour. Med., 1915, viii, 278.

found the pituitary increased in weight; in the case of goiter showing a hyperplasia of chromophil cells, an increase of colloid in the interglandular cleft, but unchanged in Addison's disease and status lympaticus. He advanced a theory of explanation of the secretary mechanism of the hypophysis which need not be discussed here.

Riese[66] reports favorable results[67] from the use of hypophysis extract in asthma, comparable to those obtained by the use of epinephrin. Similar results had been obtained previously by Borchardt (Riese).

Numerous case reports appear in the literature indicating a favorable effect following the use of hypophysial extract in diabetes insipidus. Grøndahl[17] reports a case of diabetes insipidus accompanying hypophysial tumor in a 16-year-old subject who showed alimentary glycosuria, as well as polyuria and infantilism, and subsequently developed evidences of acromegaly. The polyuria was reduced from the neighborhood of 6 liters a day to about 2 liters by injections of pituitary extract.

Hoppe-Seyler[68] reports a case in which the urinary output ranged from 4 to 7 liters daily and the specific gravity of the urine was 1.002, treated by pituitary extract. Subcutaneous injections of pituitary extract repeatedly caused temporary reduction of the total urine to between 1 and 2 liters in twenty-four hours.

Graul[69] reports a similar case in which extract from the pars intermedia and posterior lobe was given hyperdermically with success.

Metzfeldt[70] reports three patients with diabetes insipidus, one of whom showed improvement when treated with pituitary extract. This case, which Motzfeldt reports in extenso, is particularly interesting in that the patient appeared to be benefited by taking hypophysial gland by mouth. It was necessary for him to take from five to seven glands

66. Riese, E.: Zur Wirkung des Hypophysenextraktes bei Asthma bronchiale und zur Asthmatheorie, Berl. klin. Wchnschr., 1915, lii, 768.

67. It is very easy to understand that epinephrin produces a favorable effect in asthma, but it is difficult to understand why pituitary extract should produce a favorable effect. Theoretically it should produce an unfavorable effect, because it constricts smooth muscle quite independently of the innervation. Riese's results cannot be accepted until corroborated.

68. Hoppe-Seyler, G.: Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextrakt, München med. Wchnschr., 1915, lxii, 1633.

69. Graul, G.: Ueber einen mit Hypophysin-Höchst erfolgreich behandelten Fall von Diabetes insipidus, Deutsch. med. Wchnschr., 1915, xli, 1095.

70. Motzfeldt, K.: The Pituitary Gland and Diuresis. I. Diabetes Insipidus and Its Relation to the Hypophysis Cerebri. II. Studies on the Action of Pituitary Extract, Especially on Diuresis, Blood Pressure and Nitrogenous Metabolism in Relatively Healthy Men, Norsk Mag. f. Laegevidensk., 1915, xiii, 1305.

at a time, raw or dried and powdered, in order to obtain an effect comparable to "one quarter of a syringe full of commercial extract."

Von Konschegg and Schuster[71] have obtained well-marked diminution in urinary output by the use of pituitary extract injections in both animals and man. The best results they obtained in human beings suffering from primary idiopathic diabetes insipidus. Their animal material was rabbits.

Pollock[72] reported four cases of hydrocephalus accompanied by adiposity and tapering hands as probable examples of hypopituitarism, caused by the increased intracranial pressure on the hypophysis.

THYMUS

Badertscher[73] finds that the thymus of the pig is of both ectodermal and entodermal origin. The ectodermal derivative, he thinks, is constant and forms the "superficial thymus." Kastschenko[74] (1887) and Zötterman[75] (1911) also derive the thymus of the pig from both ectoderm and entoderm.

In the guinea-pig and mole[76] the thymus has also been traced to both ectoderm and entoderm, but appears to be purely entodermal in the other higher mammals investigated.

Marine[77] points out the frequency of duct-like spaces or tubules in the thymus of dogs. He was able to find them in 21 per cent. of the animals examined, but in only one human thymus out of a total of 126. Marine believes that these duct-like tubules are closely related in their origin to the Hassall corpuscles, both springing from the "embryonic thymic epithelial tubules and cords." He considers that in the case of the Hassall corpuscles the involutionary change took place before the differentiation into tubules occurred; in the case of the tubules differentiation occurred before the involutionary process began.

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71. Von Konschegg, A., and Schuster, E.: Ueber die Bllinflussung der Diurese durch Hypophysenextrakte, Deutsch. med. Wchnschr., 1915, xli, 1091.

72. Pollock, L. J.: Hypopituitarism in Chronic Hydrocephalus, Jour. Am. Med. Assn., 1915, lxiv, 395. There have appeared in the literature a number of cases of this nature. Indeed the diagnosis of hypopituitarism is frequently made in fat children who are otherwise normal, merely because they are fat. In this connection it is necessary to remember that many mentally defective children, and among them hydrocephalics, lead of necessity vegetative existences and receive diets high in carbohydrates. Consquently, they are especially prone to become fat.

73. Badertscher, J. A.: The Development of the Thymus in the Pig. I. Morphogenesis, Am. Jour. Anat., 1914-1915, xvii, 317.

74. Kastschenko: Arch. f. mikroskop. Anat., 1887, xxx; cited by Badertscher.

75. Zötterman, Agne: Anat. Anz., 1911, xxxviii, 514.

76. Ruben, R.: Anat. Anz., 1911, xxxix, 571.

77. Marine, D.: The Frequency of Duct-Like Spaces in the Thymus Gland with Remarks on the Formation and Fate of Hassall's Corpuscles, Cleveland Med. Jour., 1915, xiv, 186.

Hart[78] also has made a study of the Hassall corpuscles. He states that they are without doubt derivatives of the epithelial elements of the thymus. On this point there is a very general agreement among all authors, although it has been maintained by some investigators that the Hassall corpuscles take origin from the endothelium of blood vessels (Afanassiew,[79] Barbarossa[80]). According to Hammer,[81] Hart and others the Hassall corpuscles are formed by a coalescence of the thymus reticulum (the epithelial element) very much as giant cells are formed about foreign bodies. Hart states, further, that Hassall's corpuscles are continually being formed so long as the thymus reticulum continues to exist. In this sense, then, the Hassall corpuscles are an index to the functional activity of the thymus. Hart is careful to state that he does not regard the Hassall corpuscles as the secretory element or representing the secretory mechanism of the thymus, as some writers on this subject have done (Magni[82] Mensi,[83] Livini[84]). He regards the epithelium of the thymus (the so-called reticular cells) as the true secretory element and the Hassall corpuscles merely as the index to the amount of epithelium present. "In a word, it is possible to estimate the functioning energy of the thymus by the kind and number of the Hassall corpuscles . . . . and so draw conclusions in regard to the condition of the organ at the time of death." The formation of Hassall corpuscles is most active in childhood, and in pathologic conditions in which the thymus function is increased.

Cases of congenital status thymolymphaticus have been reported by Hedinger[35] (12 cases), Kayser,[86] Flügge,[87] Somma[88] and Durante,[89] but according to Schridde[90] it is not certain that they are all true cases, for, in the majority, data essential to the diagnosis are lacking, such as weight of the thymus or evidences of status lymphaticus outside the thymus itself. Schridde's[96] paper consists of a report of three cases of congenital status thymolymphaticus. In one case the thymus weighed 19 gm., in the second 24 gm., in the third 26 gm. The histo-

78. Hart, C.: Thymusstudien. IV. Die Hassallschen Körperchen, Virchows Arch. f. path. Anat., 1914, ccxvii, 239.
79. Afanassiew, B.: Arch. f. mikroskop. Anat., 14, 1877.
80. Barbarossa: Pediatria, 1911, Series 2, xix, 457.
81. Hammar, T. A.: Fünfzig Jahre Thymus Forschung, Ergebn. d. Anat. u. Entwicklungsgesch., 1910.
82. Magni: Arch. f. Kinderh., 1903, xxxviii, 14.
83. Mensi: Pediatria, 1903, xi, 65.
84. Livini: Cited by Mensi (Footnote 83).
85. Hedinger: Jahrb. f. Kinderh., New Series, vliii, 308.
86. Kayser, J.: Diss., Giessen, 1895.
87. Flügge: Vierteljahrsschr. f. gerichtl. Medizin, 1899, Series 3, xvii.
88. Somma: Arch. de patolog. infant, 1884.
89. Hedinger: 310.
90. Schridde, H.: Der angeborene Status thymolymphaticus, München. med. Wchnschr., 1914, lxi, 2161.

logic picture of the thymus in all three cases was identical with that described by Schridde as characteristic of the thymus of postnatal status lymphaticus. In all three cases hyperplasia of the medulla of the thymus was present, and the lymph follicles of the spleen were enlarged so that they were visible to the naked eye and in two of the cases the follicles of the intestines were also macroscopically visible. All three were excellently nourished infants. The mother of one of them died of eclampsia soon after the birth of the child and showed at necropsy the lesions of status thymolymphaticus, a coincidence which at once suggested the possibility that the pathologic condition was hereditary. Schridde also examined the thymus gland in about fifty stillbirths not the subject of status lymphaticus and found that the difference in weight of the thymus at birth is considerable, varying from 5 to 20 gm.

The average which Hammar gives for the weight of the thymus in the normally sized child at birth is 13.26 to 14.4 gm.

It is well established that the thymus either continues to persist or undergoes a reviviscence in certain diseases, as, for example, very commonly in exophthalmic goiter and with considerable frequency in Addison's disease and myasthenia gravis.

Hart[91] reports two cases of myasthenia gravis and discusses at some length the relationship of the enlarged thymus to the disease. He thinks the enlarged thymus of myasthenia gravis is a persistent thymus which has undergone hyperplasia, as the persistent thymus, in his opinion, tends to do, and that the aggregations of round cells are lymphocytic infiltrations. He attaches a twofold significance to the enlargement of the thymus in myasthenia. In the first place, he believes it indicates that the affected individual has the lymphatic constitution; in other words, is constitutionally inferior and, therefore, predisposed from birth to the development of such disturbances as exophthalmic goiter and myasthenia gravis. In the second place, Hart believes the thymus in myasthenia gravis exerts a pathologic function and is frequently, if it is not always, the cause of the disease. He states that removal of the hyperplastic thymus cures myasthenia gravis, basing his statement apparently on a single case in which the thymus was removed by Sauerbruch,[92] but at the same time admits that there are cases of myasthenia gravis without hyperplasia of the thymus, a fact which is well known. He endeavors to extricate himself from the dilemma caused through this admission by saying that after all an enlarged thymus is only one of numerous stigmata of constitutional

91. Hart, C.: Thymusstudien. V. Thymus befunde bei Myasthenia gravis pseudoparalytica, Virchows Arch. f. path. Anat., 1915, ccxx, 185.

92. Reference not given by Hart.

inferiority and that absence of enlarged thymus does not mean that the subject of myasthenia may not be constitutionally inferior, and in the second place that the thymus, though involuted, may exert a deleterious influence, citing that now well-worn case of von Haberer's, in which great improvement took place in a patient acutely sick with exophthalmic goiter, when a part of the retrosternal fat body was removed. Hart seems to be attempting to transfer his theories of thymus function in exophthalmic goiter to the thymus in myasthenia gravis. His reasoning is not clear and his interpretation of the facts seems to be tuned to his theory. The important point in his article is his statement that removal of a hyperplastic thymus cures myasthenia gravis. The truth or falsity of this statement should be investigated.

Funk and Douglas,[93] on the other hand, call attention to the complete disappearance of the thymus in pigeons suffering from beriberi. Their studies are limited to eight pigeons, apparently uncontrolled. Although the thymus is supposed to persist throughout life in the pigeon, Funk and Douglas were unable to find even microscopic rests of the thymus in their beriberi pigeons. In addition to disappearance of the thymus they found changes in other organs of internal secretion. The thyroid showed a marked degeneration in two instances and in a third signs of inflammation. The pituitaries also showed degenerative changes. (Their findings in the pituitaries can scarcely have any value because of their method of preparation for histologic study, which must have made accurate histologic interpretation impossible.) The ovaries were reduced in volume: the testes, atrophied. The pancreas was small and showed areas of degeneration. The spleen also was diminished in size and showed absence of the malpighian bodies. The ages of the birds were not given.

The work of Funk and Douglas was assailed by Williams and Crowell.[94] These authors found that in human beings having beriberi involution of the thymus does not always occur. In some cases the thymus was found actually enlarged and in others even status lymphaticus present. In a beriberi subject of 13 years the thymus weighed 28 gm.; in another 18 years old, 12 gm. Their experimental study was made on sixteen chickens having beriberi. The thymus had disappeared in seven of the chickens, was atrophied in five, and was slightly if at all altered in four. There was no evidence of a relationship between the severity of the disease and the degree of atrophy of the thymus. Thymus tissue was fed to the beriberi birds without any effect. Williams and Crowell concluded that there is no fundamental

93. Funk, C., and Douglas, M.: Studies on Beriberi. VIII. The Relationship of Beriberi to Glands of Internal Secretion, Jour. Physiol., 1914, xlvii, 475.

94. Williams, R. R., and Crowell, B. C.: The Thymus Gland in Beriberi, Philippine Jour. Sc., 1915, x, 121.

connection between atrophy of the thymus and beriberi, and if a protective influence against beriberi is exerted by the thymus, as Funk in a previous paper had maintained, it is due to the pyramidon and purin derivatives which are present in large amounts in thymus tissue.

Fenger[95] has made chemical studies of the fetal thymus to determine whether certain substances are present in it which are found in the postfetal thymus. He discovered that the fetal thymus contains nucleic bodies and phosphates in the same proportions as the glands of young growing animals. For this reason he inferred that the gland is active at least three months before birth. He points out incidentally that fetal animals have more thymus tissue per unit of body weight than animals after birth.

In the two or three years which preceded the period covered by this review, appeared the extensive publications of Klose and Vogt,[96] Klose, and of Matti[97] on the physiology of the thymus gland. Their experimental work indicated that the thymus was essentian to life, had a profound influence on the growth and development of the body and presided especially over the metabolism of bone. Their thymectomized animals not only showed marked disturbances of growth, but developed rickets and well-marked changes in the thyroid and suprarenals. Klose and Vogt, and subsequently Klose, writing independently, reported in addition extensive lesions in almost all the organs, especially in the nervous system, which they referred to loss of the thymus, and even saw in the behavior of their thymectomized dogs a condition of "thymic idiocy." The work of these investigators has had great influence on scientific opinion and rightly or wrongly has elevated the thymus to a position of great importance among the organs of internal secretion. During the past two years, however, some experimental work has appeared with results at variance with theirs, notably the work of Pappenheimer and Nordmann.

Pappenheimer[98] removed the thymus from rats, aged 3 weeks or less, controlling from the same litters. His original material consisted of twenty-six litters, making a total of 118 rats, eighty-three of which were thymectomized; but owing to an epidemic of dysentery his material became reduced to twenty thymectomized rats and their controls. The period of observation after operation ranged from forty-five to 131 days. Pappenheimer found that removal of the thymus does not produce disturbance in growth or development. No constant pathologic changes were found anywhere, not in any of the organs of inter-

95. Fenger, F.: On the Size and Composition of the Thymus Gland, Jour. Biol. Chem., 1915, xx, 115.

96. Klose and Vogt: Beitr. z. klin. Chir., 1910, p. 69.

97. Matti, H.: Ergebn. d. inn. Med. u. Kinderh., 1913, x, 1.

98. Pappenheimer, A. M.: Further Experiments on the Effects of Extirpation of the Thymus in Rats, with Special Reference to the Alleged Production of Rachitic Lesions, Jour. Exper. Med., 1914, xx, 477.

nal secretion. He serial sectioned the neck and thoracic tissues of his thymectomized animals for thymus rests, thus proving their absence in the twenty animals which formed the basis of his report. Since his experiments are probably the only ones in the higher mammals in which thymus rests were proved to be absent, his negative results have the value of positive experiments.

Nordmann[99] had already published two sets of thymus extirpation experiments in dogs. His latest contribution consists of the results of thymectomy experiments performed on eight litters of puppies in the second week of life. He used the operative method of von Basch, which may be called the standard for excision of the thymus, and the intratracheal insufflation of Meltzer. The puppies were fed on a mixed diet and were allowed complete freedom out of doors. He killed them at various periods after thymectomy in order to avoid the error of overlooking transitory changes. Some of them he let live for more than a year. His thymectomized dogs developed no symptoms or pathologic changes of any sort whatsoever. The necropsies revealed no thymus rests in a single instance, although a particularly careful search appears to have been made.

Nordmann's results in this set of experiments have especial importance because in his previous experiments in thymus extirpation he had obtained muscle weakness, abnormal gait with the forelegs thrown wide apart, fatigue, infections of the skin, with loss of hair, and circulatory disturbances, of which dilatation of the heart was the chief. The conclusion which he had drawn from his previous experiments was that the thymus is an important organ of internal secretion, possibly essential to life, having to do especially with the nutrition, regulation of the heart's action and resistance to infections. In the light of his recent work he now concludes that his former results were due to other causes than deprivation of thymus function, for example, infection, and that the thymus is not essential to life and its removal in young dogs is meaningless.

It should be added that Nordmann removed the spleens from several animals, as well as the thymus, without the discovery of any pathologic developments such as Klose described. One female dog deprived of both spleen and thymus bore normal puppies.

Nordmann suggests that the results of the thymectomies obtained by Matti and Klose may have been due to domestication. He charges Klose with the use of an inbred type of dog, particularly liable to the spontaneous development of rickets.

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99. Nordmann, O.: Experimentelles und Klinisches über die Thymusdrüse, Arch. f. klin. Chir., 1914, cvi, 172; Deutsch. med. Wchnschr., 1914, xl, 1702.
100. Klose, H.: Thymusdrüse und Rachitis, Centralbl. f. allg. Path. u path. Anat., 1914, xxv, 1.

Klose,[100] however, has come forward with further experiments performed on goats, swine and rats, which have yielded results similar to those obtained by him previously in dogs and rabbits.

The thymus in the swine, as in other hoofed animals, is a large organ situated both in the thorax and neck, which can be removed only with difficulty and never completely (Klose). Whatever changes occur in swine or goats after operation must be, therefore, the result of partial thymectomies. Klose states that swine must be operated on between the fourth and sixth week, if symptoms of thymus deficiency are to be obtained. Signs of rachitis, such as the formation of a rachitic rosary, beading of the ribs, spontaneous fractures of the extremities and disturbances in gait, appear two to three months after the operation, but are transitory, disappearing entirely. Klose's explanation of the transitory character of the symptoms in swine is that the thymus rest which was left, completely regenerating in a short time, raises thymus function to its normal level and, consequently, causes the symptoms due to diminished function entirely to disappear. His results in goats were analogous to those in swine; in goats the thymus must be extirpated in the fourth week, if pathologic changes are to be obtained.

Klose removed the thymus from the rat on the fourteenth day. His first experiments he states were negative, or at least the ensuing changes were transitory. "Many broods behaved in a refractory manner like many kinds of dogs." Klose explained this phenomenon on the ground that thymus rests were present in the thyroid, which underwent functional hypertrophy. Many animals which were free from these rests died of cachexia on an average of from six to ten weeks after the operation and the bones of these animals showed severe grades of rickets.

Klose finds the thymus in the rat is essential to life. If an animal sufficiently young at the time of operation does not die after thymus removal, the thymus, according to Klose, cannot have been completely removed.

Klose had previously advanced the theory that the spleen was closely related in its function to the thymus and normally assumed the function of the thymus when the latter underwent physiologic involution. He explained the failure of thymectomies performed late (after the fourth week) in dogs to awaken characteristic symptoms on the supposition that the spleen had been allowed time enough to assume sufficient of the thymus' function to prevent them from developing. This theory of the interrelationship of thymus and spleen was founded largely on fancy and had already been attacked and disproved and its falsity admitted finally by Klose himself. The object of Flesch's

experiments, which are about to be described, was to investigate the relationship between the thymus and spleen.

The spleen varies in weight very considerably among normal rats, so that a difference of as much as 7 gm. in the weight of the spleens of two rats of equal body weight has no significance, even though the animals come from the same litter (Flesch). Flesch[101] used rats, the youngest of which were four weeks old at the time of operation, and killed them from one to four weeks afterwards, or else allowed them to live until death occurred spontaneously in five to seven weeks. Each operative rat had a control.

Flesch found that complete removal of the thymus in the rat is usually impossible because of the presence of microscopic rests of the thymus in the neck, which cannot be found at the time of the operation. But he discovered that the rats having thymus rests did not react differently to a loss of the thymus from those rats in which no rests were found at the subsequent necropsy; for the rats in which cervical rests were present died spontaneously five to seven weeks after the operation, with but two operations, in one of which, when killed eighty days after the operation, an extremely large thymus rest was found, and in the other the spleen showed sufficient divergence from the normal, in Flesch's opinion, to account for the animal's survival! Flesch explained the development of symptoms in the presence of thymus rests by the conjecture that the small thymus particles which escaped removal reached a functional capacity too late to replace the main body of the thymus which had been removed. As might be expected, the thymus rests were found in the neighborhood of the parathyroids.

In this connection it is interesting to note Flesch's statement that the thymus rests sometimes showed signs of regeneration and sometimes degenerative changes. Klose, Fulci and Aschoff have maintained that a microscopic thymus rest left after incomplete thymectomy would regenerate until it reached the size of the original gland.

Flesch corroborated in the main the changes in the rat which Klose had reported. For eleven days after the operation no symptoms appeared ("latent period"); from the eleventh to the twenty-eighth day there occurred the "stage of adiposity," which was followed by the "stage of cachexia," ending in the death of the animal. But Flesch found no characteristic changes in the spleens. Enlargement of the follicles was almost always present and in the end stages an increase in amount of splenic pulp. Often, however, there was terminal sclerotic atrophy. Large cells of the megalokaryocyte type were fairly numerous. Flesch concludes that the spleen in the thymectomized animals

101. Flesch, M.: Experimentelle Thymusstudien. I. Teil. Thymus und Milz bei der Ratte, Beitr. z. klin. Chir., 1915, xcv, 376.

is in a state of increased function, which is not specific in character, but an expression of a general reaction on the part of the whole body to the loss of the thymus.

Adler[102] studied the relationship between thymus function and development in the frog. He extirpated the thymus by means of the galvanocautery from 950 tadpoles, but encountered an extremely high mortality, so that the number of surviving thymectomized animals fell to thirty-two within a week of the operations, and by the end of three months, to twenty animals. At that time they were killed and examined. The thymus proved to be completely extirpated in only three frogs; in five it was found that only one lobe had been removed and in the remaining twelve frogs that portions of both lobes were still present. None of the operative animals showed abnormal growth or development. The testicles of the three thymus-free animals were larger than the testicles of the controls. The pineals and hypophyses of these three frogs showed no changes, but the thyroids showed hyperplasia, with infoldings of the epithelium and diminished colloid. Adler concluded from his experiments that an interrelationship exists in the frog between thymus and thyroid and between thymus and testis. But since his conclusions are actually based on observations in only three animals, they cannot have much value.

Tongu[103] performed thymus transplantations in dogs and rabbits. He found the most favorable place for transplantation was in the peritoneal cavity. There an autotransplant might withstand absorption for as long a period as two months. He found the thymus transplanted into the spleen, abdominal wall or subcutaneous tissues was quickly absorbed; no signs of regeneration were evident. In all of his animals he created a thymus deficiency by removal of the gland in whole or in part at the time of or prior to the transplantation. His material consisted of twenty dogs and seventy rabbits, but the number of his successful experiments was exceedingly small.

Although the most extraordinary results have been reported following transplantation of the thymus, it is now well established that even thymus autotransplants cannot escape absorption for more than a limited period of time.

Hewer[104] has conducted feeding experiments on rats using thymus tabloids and the dried gland. She found that large amounts of the

102. Adler, L.: Metamorphosestudien an Batrachierlarven. I. Exstirpation endokriner Drüsen. B. Exstirpation des Thymus, Arch. f. Entwcklngsmechn. d. Organ., 1914, xl, 1.

103. Tongu, Y.: Recherches expérimentales sur la transplantation du thymus (Première étude), Mitt. a. d. Med. Fakult. d. k. Univ. zu Tokyo, 1915, xiv, 259.

104. Hewer, Evelyn: The Effect of Thymus Feeding on the Activity of the Reproductive Organs in the Rat, Jour. Physiol., 1914, xlvii, 479.

fresh gland were necessary to produce results and that males were more susceptible to thymus feeding than females. The feeding of both parents produced marked retardation in the sexual maturity of the offspring, but the length of the period of gestation was unchanged. If large doses of the thymus were given to the male rats, the structure of the testis was affected, degenerative changes taking place in sexually mature animals and retardation in development of the testis in animals not yet sexually mature. By giving large amounts of thymus Hewer was able to produce a condition which she calls "hyperthymism." The testes of these animals showed an absence of the Sertoli cells, and in the later stages degenerative changes in the sperm cells with diminished numbers or complete absence of spermatozoa. To produce the condition of "hyperthymism" from 2 to 5 gm. per day of thymus substance was given. No breeding took place if either the male or the female had been treated with large doses of thymus.

M'Neil[105] advances the hypothesis that status lymphaticus is an anaphylactic condition. He regards individuals having status lymphaticus as constitutionally anaphylactic and as reacting in an exaggerated manner to all infections. "Status lymphaticus is an abnormal condition in the body in which, if anaphylactic phenomenon occur, they do so in an exaggerated way." M'Neil furnishes no experimental evidence in favor of his hypothesis, which is pure speculation.

Paton had previously found that the testes of young guinea-pigs hypertrophied and Soli that they atrophied after thymus extirpation. Halnan and Marshall[106] in their turn have investigated the relation of thymus to testis in guinea-pigs and found that neither hypertrophy nor atrophy takes place after removal of the thymus. They confirmed the well-established fact that castration is followed by thymus persistence. Their thymectomized animals showed no abnormalities of growth or development, nor did removal of both thymus and testes in young guinea-pigs alter the growth of the animal up to the time of sexual maturity.

Hatai[107] has conducted a very painstaking investigation in the white rat of the effects of castration on the growth and the weight of certain organs, among them those of internal secretion. The most marked effect of castration on any of the organs of internal secretion was on

105. M'Neil, C.: Anaphylaxis and Status Lymphaticus: Their Relation to Intensified Types of Disease in Infancy and Childhood, Edinburgh Med. Jour., 1914, New Series, xiii, 38, 120.

106. Halnan, E. T., and Marshall, F. H. A.: On the Relation Between the Thymus and the Generative Organs and the Influence of These Organs on Growth, Proc. Roy. Soc., 1914, xxxviii, Series B, 68.

107. Hatai, S.: The Growth of Organs in the Albino Rat as Affected by Gonadectomy, Jour. Exper. Zool., 1915, xviii, 1.

the hypophysis. No change in the weight of the hypophysis was noted after spaying or semispaying, but after castration a marked increase in weight took place. No obesity occurred in castrated animals if compensatory growth of the hypophysis had developed. Hatai noted the same tendency of the thymus to persist after castration that has been noted by other authors.

Bompiani[108] confirms the findings of Fulci[109] in regard to the capacity of the thymus to regenerate after pregnancy. Pregnancy causes the thymus to involute, but, as soon as pregnancy is interrupted, the thymus begins to regenerate. Bompiani shows in addition that lactation causes the thymus to involute, or at least keeps the thymus in a state of involution, but that as soon as lactation is stopped, regeneration makes its appearance. Many authors have described regeneration of the thymus: after Roentgen ray (Rudberg[110]) (Jonson[111]); hunger (Jonson[111]); pregnancy (Fulci[112]); partial extirpation (Friedeleben,[113] Klose,[114] Fulci,[112] Aschoff,[115] etc.). Some investigators have failed to find signs of regeneration in rests left at operation (Hammar,[116] Adler,[117] Pappenheimer[118] and others). The question of the behavior of the thymus after partial excision is open to further investigation.

During the past two years Hammar has made at least three contributions to the subject of thymus pathology. The first paper[119] cannot be located and therefore is not included in this review.

The first of the two available papers of Hammar's[120] is a critical study of fourteen thymus glands taken from cases in which the diag-

108. Bompiani, G.: Der Einfluss des Säugens auf die Restitutionsfähigkeit des Thymus nach der Schwangerschaft (Vorläufige Mitteilung), Centralbl. f. allg. Path. u. path. Anat., 1914, 929; L'influenza dell' allattamento sulla capacità di reintegrazione del timo dopo la gravidanza, Gazz. internaz. di med., 1915, xviii, 65.

109. Fulci, F.: Centralbl. f. allg. Path. u. path. Anat., 1913, xxiv, 968.

110. Rudberg: Arch. f. Anat., 1907, 123; On Thymus Involutionen Diss., Upsala, 1910.

111. Jonson: Arch. f. mikroskop. Anat., 1909, lxxiii, 390.

112. Fulci, F.: Deutsch. med. Wchnschr., 1913, xxxix, 1776.

113. Friedeleben: Die Physiologie der Thymusdrüse in Gesundheit und Krankheit vom Standpunkte experimenteller Erforschung und klinischer Erfahrung, Frankfurt, 1858.

114. Klose: Neue Deutsche Chirurgie, Enke, Stuttgart, 1912.

115. Aschoff: Tr. Internat. Cong. Med., 1913, Lond.; 1914, Sect. iii, Gen Path. and Path. Anat., Part 2, 131.

116. Hammar, J. A.: Arch. f. d. ges. Physiol., cx.

117. Adler: Arch. f. Entwcklngsmechn. d. Organ, 1914, xl, 1.

118. Pappenheimer: Jour. Exper. Med., 1914, xx, 477.

119. Hammar himself refers to this article, Mikroskopische Analyse der Thymus in 21 Fällen Basedowscher Krankheit, Beitr. z. klin. Chir., 1915, but it is not in that journal.

120. Hammar, J. A.: Mikroskopische Analyse der Thymus in 14 Fällen sogenannten Thymustodes, Ztschr. f. Kinderh., 1916, xiii, 153.

nosis of "thymus death" was made, with the special object of determining the truth or falsity of certain of the existing beliefs in regard to the pathologic changes in the thymus in that condition.

For full exposition of the opinions of various writers on the subject of the pathology of the thymus in status lymphaticus the reader is referred to Hammar's original article. Suffice it here to point out that certain pathologists have taken the position that the hyperplastic thymus, or more particularly the thymus of "thymus death," presents typical pathologic changes, consisting in (1) an altered relation of medulla to cortex, (2) a change in the number, size and histologic characters of the Hassall corpuscles, and (3) the composition of the medulla. Hedinger in 1906 directed attention to the occurrence, in cases of "thymus death," of a broad medullary and narrow cortical zone, and Schridde[121] writes that the most important feature of the hyperplastic thymus is hyperplasia of the medulla, with hypoplasia of the cortex, and further, that the Hassall bodies are almost always exceedingly large and composed of fat-containing protoplasm without nuclei. In the more recent edition of Aschoff's book (1911) Schridde distinguishes two types of hyperplastic thymus, one in which medulla and cortex are both hyperplastic; the other, far the commoner of the two, in which medulla is hyperplastic and cortex hypoplastic. The hyperplasia of the medulla is characterized by an actual increase of the reticular cells (the undoubted epithelial element) and by the presence of large forms of Hassall corpuscles, though the total number per unit of thymus substance is diminished. In regard to the thymus of "thymus death," Schridde states specifically that, excepting those rare cases in which the thymus operates mechanically, hyperplasia of the medulla and hypoplasia of the cortex are invariably present. While not entirely accepting Schridde's conclusions, Hart finds medullary hypertrophy and considers the cause to be an active proliferation of the epithelial cells. His views in regard to the excessive production of Hassall corpuscles in conditions of excessive function of the thymus have already been discussed. Though other writers (Wiesel, Pappenheimer and others) have expressed dissenting opinions, nevertheless the dogmatic teachings of the Schridde school have received wide acceptance and are frequently quoted in the experimental literature on the thymus gland (Matti, Klose[122] and others). It is the truth or falsity of these views which Hammar seeks to investigate.

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121. Schridde: Aschoff's Pathology, Ed. 1.

122. As Hammar points out, the description which Klose gives of the pathologic changes in the thymus of status lymphaticus is Schridde's description almost word for word. See Neue Deutsche Chirurgie der Thymusdrüse, p. 113.

Before taking up Hammar's paper, however, it is necessary to call attention to the special methods of study used by him in this investigation, which gives to his results a mathematical accuracy. The exact amount of parenchyma (minus the fat and connective tissue) he was enabled to estimate by means of serial sections and reconstructions and in the same manner to determine the exact relation of medullary to cortical substance.[123] The Hassall corpuscles he counted.

At the beginning of his paper Hammar points out that although it is popularly supposed that the enlargement of the thymus in "mors thymica" is constant, statistics prove that such is by no means the case, for the weight of the thymus may be normal or even subnormal in that condition. Thirteen of Hammar's series of fourteen thymus glands were taken from children whose ages ranged between 9 days and 16 years. The remaining gland was that of an adult. Of the thirteen children's glands, only two were enlarged; the others showed amounts of parenchyma within normal limits. The two enlarged thymus glands had increased amounts of cortex; the medulla in one was larger than normal, though not in proportion to the cortex, and in the other lay within normal limits. The cortico-medullary index (cortical tissue, medullary tissue) was, therefore, high in both instances. (A high cortical medullary index is normal for childhood.) Both thymus glands showed subnormal numbers of Hassall's corpuscles; the very large and calcified forms were absent. A lymphatic infiltration of the medulla was present in both. Of the eleven thymus glands of normal size, one showed signs of accidental involution and was excluded from further consideration. In the remaining ten glands there was diminished parenchyma in all and a high cortico-medullary index in six. The very large and the calcified Hassall corpuscles were also absent in all. Infiltration of the medulla with lymphocytes was found in eight. In no two of the ten glands were all the characters enumerated the same.

The study of these thirteen glands showed it was not possible to distinguish any fixed type and, in fact, in the majority of the glands the variations were within normal limits. There seemed to be no morphologic ground on which to rest a theory of hyperfunction or dysfunction.

Hammar's second paper is an analysis of the mechanical theory of thymic asthma in the light of the study of the form and topographical relations of the thymus gland. Grawitz in 1888 put forward the idea that it was possible for the thymus to become wedged between the

123. Hammar, J. A.: Methode, die Menge der Rinde und des Marks des Thymus, sowie die Anzahl und Grösse der Hassallschen Körper zahlenmässig festzustellen (unter besonderer Berücksichtigung der Verhältnisse beim Menschen), Ztschr. f. ang. Anat., 1913-1914, i, 311.

upper part of the sternum and the vertebral column in such a way as to compress the trachea at that point, causing death from asphyxia. The space between the upper portion of the manubrium and spine has been known ever since Grawitz's publication as "the critical space of Grawitz." Since then other investigators (Barack,[124] Strassmann, Flügge[125]) have described a second vulnerable spot, where the trachea may be compressed by the hyperplastic thymus, namely, the point of crossing of the innominate artery. Hart, Wiesel, Klose and others recognize these two points as the places where compression of the trachea by the enlarged thymus is particularly liable to occur.

A considerable number of cases of thymic asthma have been described in the literature, chiefly by surgeons, in which the surgical operation or necropsy demonstrated a large thymus or even a causal relationship between the enlarged thymus and the clinical or pathologic condition. The one most prominent symptom reported in these cases has been inspiratory dyspnea with inspiratory stridor, though in some of them expiratory dyspnea was also referred to. The points of compression of the trachea were thought to be at the "critical points" already mentioned. The inspiratory dyspnea in "thymic asthma" has been explained by assuming that the thymus acts like a ball valve, being forced against the trachea at one of the two "critical points" during inspiration, in such a way as to compress it, but falling away again during expiration, permitting the trachea to expand once more. Surgeons who have operated on these patients with "thymic asthma" have observed that the inspiratory dyspnea ceased when the thymus was drawn upward into the neck, but recurred as soon as the thymus was allowed to resume its former position in the thorax; or that the inspiratory dyspnea was permanently diminished when the thymus was drawn upward into the neck and held in that position by suture of the capsule to the sternum.

Hammar's paper shows, in the first place, that the two so-called "critical points" at which it is thought the trachea may be compressed by the thymus are so close to each other, particularly in the new-born child, as to be almost identical, for the innominate artery crosses the trachea close to the upper border of the sternum. Therefore, it is useless to consider them separately. The statement that the trachea was greatly compressed immediately above the bifurcation where the innominate artery crosses is erroneous, for the innominate artery lies considerably above the bifurcation. If the trachea was actually compressed at that point by the thymus, that part of the thymus lying immediately opposite, just above the base of the heart, must have been

124. Barack: Diss. Berlin, 1894; cited by Hammar.
125. Flügge: Vierteljahrsschr. f. gerichtl. u. öffentl. Med., Sanitätswesen, 1899, Series 3, xvii; cited by Hammar.

responsible. The next point which Hammar makes is that since the thickest portion of the thymus lies at the level of the base of the heart, considerably below the so-called "critical point," the surgical maneuver of drawing the thymus upward not only could not possibly relieve dyspnea produced by pressure of the thymus on the trachea at the critical points, but would actually intensify it, since it would bring a thicker mass of thymus between the top of the sternum and the spine than was there previously. If the ascent of the thymus relieved the inspiratory dyspnea of "thymic asthma," it was proof that the point of compression of the trachea did not lie above the thickest portion of the thymus, but at or below the thickest part, in the neighborhood of the bifurcation. In reality the thymus is not forced upward into the neck with each inspiration, but recedes into the thorax, while it is during expiration that it is forced up into the base of the neck ("Rehn's phenomenon"), so that if it produced dyspnea by compression of the trachea anywhere above its thickest part, it would cause expiratory and not inspiratory dyspnea.

Thus Hammar proves that the existing notions about the mechanical compression of the trachea by the enlarged thymus are largely false. He points out, however, that his anatomical preparations indicate the enlarged thymus may exert pressure on the trachea close to the bifurcation, or on the bronchi, particularly in the new-born child, whose thymus is relatively much broader than at a later period. Hammar is careful to avoid the statement that the thymus does actually compress the trachea at these points.

It is to Hammar's painstaking investigations in regard to the thymus, which have never been shown to be wrong in a single particular, that we owe the greater part of our certain knowledge in regard to that organ. The results of his analysis of the fourteen thymus glands from cases of thymus death are probably worth more than the opinions of all those pathologists who have expressed themselves so positively on this subject, because the latter have dealt with impressions, while Hammar has worked out the facts. It is probable that there is no pathologic condition which is characteristic for the thymus of "thymic death" or status lymphaticus. Hammar makes ridiculous the controversionalists who have split hairs on the subject of the compression of the trachea by the enlarged thymus at the "critical points."

THE THYROID

Halstead[126] showed by experiments performed in 1887 and 1888 that after excision of a portion of the dog's thyroid the remainder underwent hypertrophy.

126. Halstead, W. S.: Johns Hopkins Hosp. Reports, 1896, i, 373.

Hunnicutt[127] has repeated Halstead's experiments at Halstead's own suggestion. He removed the thyroid piecemeal from thirty-nine dogs and found that in only one of them did the thyroid rest develop hyperplasia. In twenty other dogs, similarly treated, the wounds were left open to determine whether a relationship existed between hyperplasia of the thyroid and infection; but no hyperplasia resulted. Hunnicutt found that one entire lobe and three-fourths of the other lobe of the dog's thyroid could be removed without affecting the remainder of the gland. In only three of the total fifty-nine animals in which piecemeal removal of the thyroid was done did the remaining piece of gland change from the normal to the hyperplastic state, while in five of the fifty-nine dogs the thyroid, which had been found to be hyperplastic in the first place, reverted back in the interval to the normal state, that is, the thyroid rest at the conclusion of the experiment proved to be normal. Definite increase in the size of the rest was not discovered in any instance.

Hunnicutt calls attention to the great variability in the histologic structure of the thyroid of the dog. Sections taken from the thyroids before any operation had been performed showed marked hyperplasia in 32 per cent. of the animals and early signs of hyperplasia in 5 per cent. No partially thyroidectomized dog developed myxedema or tetany.

On the other hand, Basinger, who removed the thyroids from rabbits in order to produce myxedema, found that thyroid rests have a great tendency to undergo hyperplasia. "Care was taken to remove all thyroid tissue, because it is surprising how often small remnants of tissue were hypertrophic." The remnants were never more than one-tenth of the size of one of the lobes of the thyroid.

Douglas[128] examined the thyroids of pigeons, fowls, rats and rabbits to determine the extent of normal variation in the histologic structure of the thyroid in different members of the same species. He concluded that the histologic picture of the thyroid in different animals of the same species kept under the same conditions is so variable that an interpretation of experimental results based on histologic changes in the thyroid is extremely difficult.

Fox[129] reports marked variations in the thyroids of wild animals confined in the zoological garden in Philadelphia.

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127. Hunnicutt, J. A.: The Absence of Hyperplasia of the Remainder of the Thyroid in Dogs After Piecemeal Removal of This Gland; Autotransplantation of the Thyroid in Partially Thyreoidectomized Animals, Am. Jour. Med. Sc., 1914, cxlviii, 207. Halstead, W. S.: Ibid., cxlvii, 56.

128. Douglas, M.: The Histology of the Thyroid in Animals Fed on Various Diets, Jour. Path. and Bacteriol., 1914-1915, xix, 341.

129. Fox, H.: The Pathology of the Thyroid Gland in Wild Animals, Proc. Path. Soc. Philadelphia, 1915, New Series, xvii, 20.

McCarrison[130] has made comparative studies of the thyroid gland of wild rats, of white rats and mice kept in confinement and of goitrous rats, both wild and domestic. It was his observation that goiter was exceedingly rare in wild rats, but that the structure of the thyroid gland varied within wide limits and appeared to be especially influenced by altitude and season. A larger proportion of thyroids of domesticated white rats were in a state of active secretion than was the case with the thyroids of wild rats. A small proportion of white rats confined in cages developed goiter spontaneously.

Jackson investigated the effects of starvation on the thyroids of rats. He found that when young rats were held for several weeks, on a diet just sufficient for maintenance, histologic changes appeared in the thyroid; the follicular epithelium became atrophied and reduced in height, the nuclei hypochromatic and pycnotic, and in extreme cases, fragmented; the cytoplasm was more affected than the nucleus, but in some instances showed no changes, while in others it was vacuolated; the colloid appeared normal in some instances, in others disintegrated and replaced by desquamated epithelial cells. The changes just described Jackson thinks in no wise typical of hunger effects, but such as are seen in the thyroid in numerous pathologic conditions.

Jackson found also that the thyroid of the albino rat lost but little weight in acute inanition of sufficient degree to cause the body as a whole a loss of one-third of its total weight. In chronic inanition, on the other hand, the thyroid lost from 22 to 24 per cent. of its weight.

Bensley[132] also comments on the variability of the structure of the thyroid in animals and the frequency of environmental changes:

> The readiness with which the thyroid gland undergoes hyperplastic changes, its responsiveness to iodin administration, as demonstrated by Marine and his co-workers, the ease by which it may be modified structurally by dietary conditions, as shown by the work of Reid Hunt (1911), Marine, Chalmers, Watson (1907), Tanberg (1900) and Missiroli (1910), and confirmed by my recent studies on the relation of diet to hyperplasia in opossums under domestication, confirm the conclusion that there is a delicate adjustment between the functioning of the thyroid gland and general body conditions, though at present we do not know the means by which this adjustment is mediated.

In 1914 Gudernatsch[133] reported the results of his second series of feeding experiments on tadpoles. He found that when tadpoles were

130. McCarrison, R.: Nervous Cretinism, Brit. Jour. Child. Dis., 1914, xl, 508.
131. Jackson, C. M.: Effect of Acute and Chronic Inanition on the Relative Weights of the Various Organs and Systems of Adult Albino Rats, Anat. Rec., 1915, ix, 90.
132. Bensley, R. R.: The Normal Mode of Secretion in the Thyroid Gland, Am. Jour. Anat., 1916, xix, 37.
133. Gudernatsch, J. F.: Feeding Experiments on Tadpoles. II. A Further Contribution to the Knowledge of Organs with Internal Secretion, Am. Jour. Anat., 1914, xv, 431.

fed large amounts of thyroid, they emaciated rapidly and died, but when fed the proper amounts, remained alive and metamorphosed into frogs on the eighteenth day, although normally the tadpole does not turn into the frog until from 10 to 13 weeks old. The result of the premature transition of tadpole to frog was that frogs in miniature were produced, but which never ate, and died within a few days to several weeks. On the other hand, Gudernatsch found that tadpoles fed thymus or spleen grew rapidly, but showed no tendency to metamorphose into frogs. Not one of several thousands of tadpoles fed on thymus could be made to develop into a frog, though tadpoles fed on liver became frogs at the normal period. Gudernatsch, therefore, concluded that the thyroid contained some substance which specifically stimulated development (differentiation in the frog), accelerating it, but at the same time inhibiting growth, while the thymus contained some substance which accelerated growth but inhibited development, also in a specific manner, and that this substance was likewise contained in the spleen and probably also in lymphatic tissue, though to a less extent than in the thymus. The results of Gudernatsch's experiments were confirmed by Romeis[134] (Stettner).

Morse[135] undertook to determine the element in the thyroid gland which caused the changes in growth and development of the tadpole described by Gudernatsch. He excluded the lipoid of the thyroid as the possible substance by obtaining the same effects in the tadpole with lipoid-free thyroid as with untreated thyroid. He next obtained negative results with "metallic" iodin, potassium iodid, methyl iodid, iodobenzoic acid, etc., showing that inorganic iodin is not the substance in question. Iodin-bearing algae, used to determine the effect of iodin in organic combination, and starch iodate ("colloidal iodin such as exists in starch") were both without effect. Kurajeff's blood protein iodin compound ("iodalbin") was effective, however, and both thyroid derivatives, thyroglobulin and iodothyrin, gave results indistinguishable from those produced by thyroid itself. Iodized amino-acids produced less pronounced yet positive results. Morse concludes that the substance in the thyroid which produces the specific effect "concerns the iodin, which is associated in some way with the amino-acids composing the complex iodized globulin of the thyroid." He explains the effectiveness of the iodized blood albumin by its protein linkage.

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134. Romeis, B.: Experimentelle Untersuchungen über die Wirkung innersekretorischer Organe. II. Der Einfluss von Thyreoidea- und Thymusfütterung auf das Wachstum, die Entwicklung und die Regeneration von Anurenlarven, Arch. f. Entwcklngsmechn. d. Organ., 1914, xxxvii, 571; Ibid., xl, 571; Ibid., xli, 57.

135. Morse, M.: The Effective Principle in Thyroid Accelerating Involution in Frog Larvae, Jour. Biol. Chem., 1914, xix, 421.

Lenhart[136] also studied the effects of thyroid feeding on tadpoles. He gave the experimental tadpoles on alternate days desiccated thyroid taken from sheep, cattle and man (goiter cases), together with fresh pig liver, while he fed the latter substance daily without admixture of thyroid to the control tadpoles. The idea underlying the experiments was to determine whether the iodin element of the thyroid was the substance which produced the characteristic changes in the tadpoles. Accordingly, Lenhart estimated the iodin content of the thyroid powder in each instance before use. The results of Lenhart's feeding experiments were similar to those of Gudernatsch: large amounts of thyroid caused the tadpoles to emaciate and die before differentiation commenced, but smaller amounts caused differentiation to occur earlier. But Lenhart offered a different interpretation for the results obtained from that of Gudernatsch, namely, that thyroid feeding produced merely an acceleration of the normal metabolism of the tadpole, which in turn manifested itself by a more rapid development and so an earlier metamorphosis.

Like Morse, Lenhart found that nonthyroid iodin, for example, potassium iodid, produced no effect on the tadpole. The effectiveness of the thyroid feeding was, however, always in direct proportion to its iodin content, so that Lenhart concluded the iodin element in the thyroid is the active principle responsible for the changes obtained. No different effect was discovered when the human thyroid was used; if anything, human thyroid was not so potent as the thyroid of the dog.

Stettner[137] has investigated the effects on tadpoles of feeding thymus, thyroid and genital tissue (ovaries and testes). The thyroid-fed tadpoles were affected exactly like those of Gudernatsch and Lenhart. The thymus-fed tadpoles showed marked irregularities in growth and development. They tended to metamorphose late and develop into malformed frogs with short legs, large abdomens and well-developed musculature. Growth in the majority of the thymus-fed tadpoles appeared to be slightly retarded, but some, receiving extract from a particular thymus (that of a young female calf), attained a giant size. Genital gland feeding produced, in most instances, a late metamorphosis, into a thin frog with slender muscles. The combination of thymus and genital feedings caused metamorphosis at its normal time and led to the production of a normally formed frog.

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136. Lenhart, C. H.: The Influence on Tadpoles of Feeding Desiccated Thyroid Gland in Variable Amounts and of Variable Iodin Contents, Jour. Exper. Med., 1915, xxii, 739.

137. Stettner, E.: Beeinflussung des Wachstums von Kaulquappen durch Verfütterung von Thymus und geshlechtsorganen, Jahrb. f. Kinderh., 1916, lxxxiii, 154.

Stettner saw in the results of his experiments the specific effects of the organs of internal secretion. In his opinion the experiments showed that thymus and genital gland acted in an antagonistic manner and a proper admixture of both was necessary for perfect development, for, though either one given singly caused a retardation in development, their effects were the opposite in other respects. He thought it possible that the deformities of the thymus-fed tadpoles might be rachitic.

The results of the feeding experiments of Gudernatsch, Romeis, Morse, Lenhart and Stettner make certain the effects of thyroid feeding on tadpoles. But the effects of thymus feeding have not been shown so clearly. Though Gudernatsch found that thymus feeding postponed indefinitely metamorphosis in the tadpole, be obtained similar results with splenic tissue, which indicates that the effect of thymus feeding, though definite, was not specific, or at least the active substance was not limited to the thymus, and Stettner's results, which were not exactly like those of Gudernatsch, were not sufficiently uniform to permit of any definite interpretation. The exact effect of thymus feeding on the tadpole should be determined by new, suitably controlled experiments.

Basinger's[138] experiments, already referred to in connection with the question of thyroid hyperplasia, were undertaken with the view of establishing a biologiç test for the active principle of the thyroid, but were actually concerned with the determination of the effects of normal rabbit blood serum, "hyperthyroid" blood serum, standard thyroid preparations, thyroid metaprotein and Kendall's extract B on cretinized rabbits.

He was able to produce cretin rabbits in about eighty-one out of a total of 140 animals. He found certain litters more refractory than others: for example, he succeeded in obtaining cretins in 90 per cent. of some of the litters operated on, while in others in only 25 per cent. The symptoms of experimental cretinism in the rabbit corresponded to the clinical picture of cretinism in human beings. About two weeks after the extirpation of the thyroid the hair became drier, inclined to stand up and could be pulled out easily. In the third week after operation retardation in growth became noticeable. By the tenth week the average weight of the cretin rabbits was 750 gm., while that of the control rabbits was 1,400 gm. The bones showed a "pseudorickety condition' called by Hofmeister "chondrodystrophia thyreopriva" (Basinger). Still later the cretin rabbits developed potbellies and scaly eczematous-like lesions of the skin. They became slow and

138. Basinger, H. R.: The Control of Experimental Cretinism, THE ARCHIVES INT. MED., xvii, 260.

awkward in their movements and would sit for hours without moving. Sixteen cretin rabbits Basinger kept alive for more than one year.

Normal blood serum transfusions produced no effect on the cretin rabbits. But the blood serum of rabbits fed on thyroid to the point of hyperthyroidism did cause definite improvement, but less than that caused by thyroid feeding. The cretin rabbits, which were fed thyroid the moment symptoms appeared, never grew quite so large as the control rabbits, although the other signs of cretinism disappeared. Kendall's thyroid extract B had no effect. A further interesting point, which Basinger's experiments brought out, was that the cretin rabbits continued to grow after the period when growth of the normal rabbits had ceased.

During the past few years the treatment of cretinism and myxedema by thyroid transplantation has been attempted in several of the European clinics, notably in those of Kocher, Payr and Eiselberg. The transference of thyroid tissue from one individual to another is simple; the difficulty lies in making the transplanted tissue live and functionate. If this difficulty can be surmounted, the cure of cretinism and myxedema can be accomplished, instead of the approximation to complete cure afforded by oral thyroid therapy. Hence the great importance of the attempts to treat cretinism by means of thyroid implantation.

Payr points out that almost all the transplantation work on the thyroid in animals has been done with autotransplants and probably many of the poor results of thyroid transplantation in human beings have been due to the necessity of using homeotransplants. Very little experimental work in homeotransplantation of the thyroid has been done, but as the knowledge about tissue transplantation increases, tissue specificity is becoming more apparent and the number of tissues which permit of homeotransplantation is becoming correspondingly less. Payr believes the outlook for successful transplantation is more hopeful in cases in which the thyroid is deficient than in those in which the thyroid is absent. The best results, he thinks, are obtained by the use of homeotransplants from blood relatives. He advises the use of a large piece of thyroid as a transplant, rather than a small piece or several small pieces. The best sites for the transplants are probably the spleen or thymus, the latter on account of its accessibility. There are undoubtedly cases, he thinks, in which trasplantation of the thyroid brought about a favorable result, when oral therapy had failed, and a few cases in which the effect of the transplantation could be followed for years. Payr states that the therapeutic effect from

139. Payr, E.: Zur Frage der Schilddrüsentransplantation, Arch. f. klin. Chir., 1914, cvi, 16.

thyroid transplantation is more rapid and complete than from thyroid feeding, probably because more elements are present in the internal secretion of the thyroid than can be absorbed through the intestinal tract.

Payr concludes his article with the report of five of his own cases. One of his patients, an eight-year-old cretin, received in the spleen a large piece of her mother's thyroid. In the succeeding half-year she grew 12 cm., when in the three previous years she had grown only 6 cm. and her development in other respects was commensurate with her growth. Two and a third years after the transplantation the patient had a recrudescence of her myxedema, so that the results of the thyroid transplantation were not permanent. Payr's other cases were much less striking than the case just described.

Von Eiselsberg[140] reported two cases of cretinism in which he had transplanted thyroid. In a 13-year-old cretin he had made altogether six implantations of pieces of human thyroid obtained as chance offered. The favorable results following transplantation were only temporary. The other patient was similarly given three thyroid grafts and improved during a short period of observation. Von Eiselsberg also calls attention to the *éclatant* effects produced by transplantation as compared with feeding, the former being much more rapid in their development than the latter.

Kocher[141] has contributed his experiences in the treatment of myxedematous conditions by means of thyroid transplantation. The main points in his paper are the following: In no case has a complete and permanent restitution to the normal condition been accomplished in a myxedematous human subject as a result of thyroid transplantation, but in some cases definite improvement has followed, as evidenced by the fact that a smaller amount of thyroid extract was required by the patient, or that the patient himself was conscious of feeling better. He states that before making the transplantation it is necessary to give the patient a preliminary treatment with thyroid, not to make certain of the diagnosis, but to raise the patient's tissues to such a level of nutrition as to enable them to nourish the transplant after it has been received and that the donor must have an active or hyperactive thyroid. Kocher plants either a single large piece of thyroid or a number of smaller pieces and immediately after the transplantation continues the thyroid therapy by mouth in order to combat "thyroid hunger."[142]

140. Von Eiselsberg, A. F.: Zur Frage der dauernden Einheilung verpflanzter Schilddrüsen und Nebenschilddrüsen, zugleich ein Beitrag zur post-operativen Tetania parathyreopriva, Arch. f. klin. Chir., 1914, cvi, 1.

141. Kocher, T.: Ueber die Bedingungen erfolgreicher Schilddrüsentransplantation beim Menschen, Arch. f. klin. Chir., 1914, cv, 832.

142. For a discussion of the most favorable sites for the transplants consult Kocher's article (Footnote 141).

Eighteen of Kocher's patients appear to have been improved by the thyroid transplantation, while in the eighteen other patients no improvement of any kind resulted.

The experimental literature in regard to thyroid transplantation, as Payr points out, relates almost entirely to autoplastic transplantation (von Eiselsberg,[143] 1892; Enderlen,[144] 1898; Payr,[145] 1906; Salzer,[146] 1909; Cristiani). Cristiani,[147] who between the years 1894 and 1906 wrote thirty papers on the subject of thyroid transplantation, is the only investigator mentioning homeotransplantation (Hesselberg).

Hesselberg's[148] work bears immediately on this subject and consists of the direct comparison of the growth and development of thyroid homeo- and autotransplants. Her material was guinea-pigs, numbering in all seventy-five animals. Autotransplantation and homeotransplantation were performed simultaneously in pairs of animals, so that direct comparison was possible. The experimental animals were killed at various periods after transplantation and the transplanted tissues excised and sectioned. For a short time after the operation no differences in the transplants were observed. Comparatively soon, however, a destruction of the follicles of the homeotransplants was noticeable, due apparently to an invasion of lymphocytes and an ingrowth of connective tissue. The latter grew much more abundantly into the homeotransplants than into the autotransplants, remaining cellular in the latter, while it became fibrous in the former. The autotransplants developed far the better blood supply. At the end of forty-seven days the homeotransplants had practically disappeared, while the autotransplants were not only living, but showed signs of outgrowth into the surrounding tissue.

Whether homeotransplantation of the thyroid is a success or a failure when applied to human beings with thyroid deficiency cannot be answered with certainty until the fate of the transplanted human thyroid is known. Hesselberg's experiments demonstrate that in the guinea-pig the thyroid tissue transplanted from another individual survives only for a short time. The results of the homeotransplantation experiments in myxedematous human subjects, just

143. Von Eiselsberg: Wien. klin. Wchnschr., 1892, v, 81.
144. Enderlen: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1898, iii, 474.
145. Payr: Verhandl. d. deutsch. Gesellsch. f. Chir., 1906, xxxv, 503; Arch. f. klin. Chir., 1906, lxxx, 730.
146. Salzer: Arch. f. klin. Chir., 1909, lxxxix, 881.
147. Christiani: For a list of his very numerous publications on this subject, see bibliography at end of article by Hesselberg, Cora: A Comparison of Autoplastic and Homeoplastic Transplantation of Thyroid Tissue in the Guinea-Pig, Jour. Exper. Med., 1915, xxi, 164.
148. Citation given in Footnote 147.

related, point also to the same conclusion. The treatment of cretinism by thyroid transplantation up to the present time must be considered a failure and in all probability will never succeed until the problem of the overcoming of tissue specificity is solved.

Fenger[149] found that both enlarged and normal-sized human fetal thyroids contain iodin, at least during the last three months of fetal life, as do the thyroids of cattle, swine and sheep. Because the fetal thyroid contains iodin, Fenger assumes that it functionates in fetal life.

The observation was made a long time ago that the thymus is frequently enlarged in exophthalmic goiter, even in poorly nourished adult subjects whose thymus glands under normal conditions are atrophied. In 1858 Markham[150] reported a case of exophthalmic goiter showing large thymus at necropsy and Moebius[151] discussed the significance of enlarged thymus in exophthalmic goiter in his well-known monograph on that subject. But the statistical studies of the past few years, in particular those of Thorbecke[152] and Capelle[143] have shown an incidence of large thymus in exophthalmic goiter previously unsuspected. For example, Capelle's figures revealed an enlargement or persistence of the thymus in 95 per cent. of fatal cases of exophthalmic goiter and in 44 per cent. dying from other causes. Since the coincidence of large thymus and exophthalmic goiter is too frequent to be explained as accidental, the question naturally arose whether the thymus might not be actively concerned in the production of exophthalmic goiter. The possibility that this might be so was strengthened by the experimental investigations of Matti[97] and Klose,[96] which indicated, as already pointed out, that the thymus is itself one of the most important of the organs of internal secretion and that a definite interrelationship exists between thyroid and thymus in that the thyroid becomes hyperplastic when the thymus is extirpated. Still further evidence in support of a thymogenic influence in exophthalmic goiter has been supplied by surgeons, who, acting on the theory that the thymus exerted a deleterious influence, have treated patients by excision of a portion of the thymus, as well as the thyroid, or by partial excision of the thymus alone.

Numerous reports that reduction of both thymus and thyroid have caused more favorable results than those obtained from partial thy-

149. Fenger, F.: On the Presence of Iodin in the Human Fetal Thyroid Gland, Jour. Biol. Chem., 1915, xx, 695.
150. Markham: Med. Times and Gaz., May 1, 1858; cited by Hart.
151. Moebius: Deutsch. Ztschr. f. Nervenh., 1891, i, 5; Nothnagel: Spec. Pathol. u. Therapie Bas'sche Krankh., Wien., 1896.
152. Thorbecke, M.: Der Morbus Basedow mit Thymus persistenz, Diss., Heidelberg, 1905; cited by Capelle.
153. Capelle: Beitr. z. klin. Chir., 1908, lviii, 353.

roidectomy alone have appeared in the literature (Garrè,[154] von Haberer,[155] Klose,[156] Sauerbruch[157] and others). In two recent papers von Haberer[158] reports good results in a series of cases of exophthalmic goiter treated by reduction of both organs, and Halstead the beneficial effects of the Roentgen-ray treatment of the thymus in several cases of exophthalmic goiter in which the thyroids had been partially resected without much improvement. But more important with a view to the determination of the part actually played by the thymus in exophthalmic goiter are the cases treated by the excision of thymus alone, of which there are now a number in the literature (Garrè, von Haberer, Capelle and Bayer, Sauerbruch and others). Although the results in these cases of thymus resection alone are reported as favorable, in no instance has the operation been curative, and in at least two of the cases a subsequent partial excision of the thyroid was necessary. Not one of them proves that the thymus can cause exophthalmic goiter, and in fact none furnishes convincing proof that the thymus has anything whatsoever to do with the production of that disease. Nevertheless, Hart and others regard the proof established, chiefly from their interpretation of the results in these cases, that a purely thymogenic form of exophthalmic goiter exists. Hart recognizes three types of exophthalmic goiter, (1) purely thyrogenic, (2) purely thymogenic, and (3) a mixed form, though he admits that the purely thymogenic form is rare. Klose, as usual, takes the extreme position "no thymus, no Basedow."

Two hypotheses have been advanced to explain the rôle the thymus plays in exophthalmic goiter. According to one of them, that advanced by Gebele,[159] the thymus is thought to compensate for the thyroid insufficiency and for that reason to hypertrophy or at least to persist when the thyroid function becomes sufficiently affected; in other words, the thyroid is the primary cause of exophthalmic goiter and the thymus plays a secondary part. According to the other hypothesis, that of Capelle and Bayer,[160] and accepted by Klose,[161] Hart and others, the thymus is thought to have an independent pathologic function, which adds to or intensifies the symptoms produced by the diseased

154. Garrè: Verhandl. d. deutsch. Gesellsch. f. Chir., 1911, No. 1.
155. Von Haberer: Verhandl. d. deutsch. Gesellsch. f. Chir., 1913, No. 1.
156. Klose: Berl. klin. Wchnschr., 1914, No. 1.
157. Sauerbruch: Beitr. z. klin. Chir., 1912, lxxvii.
158. Von Haberer, H.: Kasuistisches zur Frage therapeutischer Misserfolge bei Morbus Basedowii, Wien. klin. Wchnschr., 1915, xxviii, 1; Over de klinische beteekenis der thymusklier (special met't oog op deh Morbus Basedowii en den status thymicus), Med. Weekbl., 1914-1915, xxi, 242.
159. Gebele: Beitr. z. klin. Chir., 1910, lxx, No. 1; Ibid., 1911, lxxvi.
160. Capelle, W., and Bayer, R.: Beitr. z. klin. Chir., 1913, lxxxvi, 509.
161. Klose: Footnote 156; Lampé Liesegang. Beitr. z. klin. Chir., lxxvii.

thyroid; that is, the thyroid and thymus share in the production of exophthalmic goiter.

Various pathologic changes in the thymus of exophthalmic goiter have been described, but none of them are constant. It is probably true that no pathologic condition of the thymus characteristic of exophthalmic goiter exists.

Von Haberer[158] states in a recent paper on this subject that results of the treatment of exophthalmic goiter by partial excision of the thymus have failed to show that a purely thymogenic form exists, although they indicate that the thymus exerts an important pathologic influence. He admits that it is not feasible to distinguish the symptoms produced by the thymus and thyroid. The effect in exophthalmic goiter of thymus reduction, in addition to thyroidectomy, is to make the subsequent course more favorable. Undoubtedly cases of exophthalmic goiter exist in which the thymus plays no part.

In the more recent of his two papers on this subject von Haberer[158] reports two more patients with exophthalmic goiter treated by the combined operation on thymus and thyroid. One of the cases had a fatal termination soon after the operation, with the extreme postoperative tachycardia now so commonly regarded as due to pathologic thymus function. Although the occurrence in this case of symptoms referable to the thymus, after a large part of the latter had been removed, appeared to speak against the theory of thymic influence in exophthalmic goiter, the necropsy, according to von Haberer, tended to strengthen the theory, since it revealed 70 gm. of thymus tissue still remaining in the thorax.

Albert Kocher's[162] paper deals with this same subject. The main points brought out are the following: Exophthalmic goiter without hyperplasia of the thyroid is unknown. On the other hand, numerous cases of exophthalmic goiter with a normal thymus have been established. The thymus undergoes late hyperplasia or revivescence in from 45 to 50 per cent. of the cases of exophthalmic goiter. Its enlargement is much commoner in young than in old subjects. The histologic picture of the thymus shows nothing characteristic to distinguish it from the hyperplasia of childhood. Thymus hyperplasia is much commoner in certain neighborhoods and in certain families than in others. If the thyroid is sufficiently reduced, thymus hyperplasia decreases. The operation for reduction of the thyroid is no more dangerous when enlargement of the thymus exists than when no enlargement is present. If the symptoms of exophthalmic goiter are obstinate, with a tendency to exacerbation, part of the thymus may be removed in addition to the

162. Kocher, A.: Ueber Basedow'sche Krankheit und Thymus, Verhandl. d. deutsch. Gesellsch. f. Chir., 1914, xliii, Part 2, p. 567.

thyroid. A pretreatment with thymus preparations or Roentgen ray may be tried, if the cases are found to react favorably to them.

Klaus[163] reports a case of exophthalmic goiter occurring in a child 9 months old. The evidences of the disease were exophthalmos, noticed by the parents in the third week, well-marked von Graefe's and Stellwag's signs, and a palpable thyroid, thought to be enlarged. The thymus was judged to be considerably enlarged because of an increase in perimanubrial dulness. The child was known to have rickets and tuberculosis. He was given a single tuberculin treatment and was not seen again for a year. But, when examined again, at the end of that time, he showed no signs at all of exophthalmic goiter; the exophthalmos and the enlargement of the thyroid were gone. Klaus reports the case as the earliest instance of exophthalmic goiter on record.

Inasmuch as exophthalmos occurs in anemic, rachitic children quite independently of exophthalmic goiter; and von Graefe's sign is occasionally seen in normal infants, and slightly enlarged thyroids in infants do not necessarily have a pathologic significance; and the size of the thymus cannot surely be determined by percussion, the case can scarcely be accepted as one of exophthalmic goiter, at least on the data furnished by Klaus. The additional fact that all signs of the disease had disappeared spontaneously after a year makes the correctness of Klaus' diagnosis still more doubtful.

The review of the literature on the thyroid cannot close without mention of the experiments of Cannon and his co-workers. In the past two years these investigators have developed at least two new methods of study of the endocrine glands, which may have farreaching results. They furnish also the first physiologic proof of hormonic interaction between two organs of internal secretion, the suprarenal and thyroid. Their experiments are among the most brilliant that have ever been done in this field of investigation.

Cannon, Binger and Fitz[164] have produced the symptoms of hyperthyroidism in cats by anastomosing the anterior root of the right phrenic nerve to the right cervical sympathetic, so that, after regeneration had taken place, the thyroid might receive a stimulation with each respiration. The six cats that were alive five months after the anastomosis had been performed showed tachycardia, diarrhea, increased excitability and accelerated metabolism. One of the cats developed exophthalmos. In the cat most affected the suprarenals were found to

163. Klaus, O.: Basedow bei einem neun Monate alten Kinde, Prag. med. Wchnschr., 1914, xxxix, 515.

164. Cannon, W. B., Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, Am. Jour. Physiol., 1914-1915, xxxvi, 363.

be three times their normal weight. In a recent paper Cannon and Fitz have shown that the symptoms just mentioned could be made to disappear by removing the thyroid on the side on which the anastomosis of phrenic and sympathetic had been originally performed.

Cannon and Cattell[165] confirmed the observation of Bayliss and Bradford, made in 1885, that an electrical change in the submaxillary gland accompanies the act of secretion and that the change is absent when secretion is not taking place. Applying the same method of investigation to the ductless glands, they found that an action current was set up in the thyroid when the sympathetic was stimulated, and similarly an action current in the suprarenal followed stimulation of the splanchnic nerve. The latent period after stimulation of both thyroid and suprarenal was considerably longer than that which followed stimulation of the salivary glands.

Applying this method of study to the thyroid gland,[166] they found again that stimulation of the sympathetic trunk in the thorax produced an action current in the thyroid gland, which did not occur when other nerves were stimulated; and that this action current remained after the superior and inferior laryngeal nerves had been cut. When the cervical sympathetic was cut, the action current still persisted though in a modified form, but disappeared entirely when the inferior cervical ganglion also was removed. Stimulation of the vagus produced no action current. Cannon and Cattell offer these experiments as proof of the sympathetic innervation of the thyroid gland. Anatomists have already traced fibers from the cervical sympathetic to the thyroid, and previous investigators have shown that atrophy of the thyroid follows severance of its cervical sympathetic nerves (Cannon and Cattell).

Cannon and Cattell[167] have also succeeded in experimentally demonstrating an interrelationship between suprarenal and thyroid. They first showed that the injection of small doses of epinephrin into the blood stream of the cat induced an action current in the thyroid. Stimulation of the splanchnic nerve, physiologically separated from the central nervous system, likewise invoked an action current in the thyroid. The action current did not occur, however, after stimulation of the splanchnic if the return of blood from the abdomen was prevented, but took place promptly when the pent-up blood was released.

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165. Cannon, W. B., and Cattell, McK.: Some Results of Studies on Electrical Changes in Glands, Am. Jour. Physiol., 1916, xl, 143.

166. Cannon, W. B., and Cattell, McK.: Some Conditions Controlling Thyroid Activity, Boston Med. and Surg. Jour., 1916, clxxiv, 138.

167. Cannon, W. B., and Cattell, McK.: III. Influence of Suprarenal Secretion on Thyroid, Am. Jour. Physiol., 1916, xli, 74.

The electrical change also failed to appear after splanchnic stimulation if the suprarenal glands had been previously removed.

"GLANDULA INSULARIS CERVICALIS": A NEW ORGAN OF INTERNAL SECRETION

Pende[168] describes a structure found in the neck of man, the dog and other animals in the last months of intrauterine life and during the first year, but not after that time, which he thinks is a hitherto unnoticed organ of internal secretion. It is made up of numerous small lobular masses, scattered about in the neighborhood of the thymus and thyroid, and especially likely to be present near the upper pole of the thymus or close to the parathyroids. Some of the separate masses are large enough to be seen with the naked eye as grayish, red particles. The total volume of the "gland" is greater than that of the parathyroids. The lobules, which are sharply separated from each other, are composed of epithelial cells, which are larger in some instances, in others smaller, than the cells of the parathyroids. The cytoplasm contains an abundance of basophilic and acidophilic granules, vacuoles and lipoid substances, while the nuclei are large and round, or in some instances small and pale staining. No connective tissue stroma is present.

Pende's reasons for thinking the structure is an endocrine gland are based solely on histologic appearances. The cells impress him as being epithelial and secretory.

It is thought that Pende's new organ of internal secretion is embryonal fat tissue. Its scattered and irregular distribution, its complete disappearance soon after birth and the comparison of the illustrations in Pende's article with sections of embryonic fat from the necks of new-born puppies makes this suggestion highly probable. Dr. Milton Winternitz[169] first expressed this view.

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168. Pende, N.: Ueber eine neue Drüse mit innerer Sekretion (Glandula insularis tervicalis), Arch. f. mikr. Anat., 1914, lxxxvi, 1., Abt., 193.

169. Winternitz, Milton: Personal communication to the author.

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